

# Genetics of the Connectome and the ENIGMA Project

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**Abstract** Here we give an overview of a worldwide effort, called the ENIGMA Consortium (<http://enigma.ini.usc.edu>), which unites scientists worldwide to determine how variants in our genetic code influence the brain, and how 12 major diseases affect the brain worldwide. At the time of writing, ENIGMA involves over 500 scientists from 185 institutions worldwide, working together on around 30 projects to discover factors that may help or harm the brain. By pooling genome-wide genomic data and brain imaging from over 33,000 people, ENIGMA has been able to identify single-nucleotide differences in the genome that are associated with differences in human brain structure and function. Given the broad interest in brain connectivity and the factors that affect it, we outline some tactics adopted by ENIGMA to discover specific genes that affect the brain; then we describe how ENIGMA is extending these methods to discover genetic influences on brain connectivity.

## Background to ENIGMA

ENIGMA (Enhancing Neuroimaging Genetics through Meta-Analysis) is a worldwide network of researchers who work together to investigate various questions about the brain. The consortium pools brain imaging and genetic data from over 200 institutions around the world. The main goals of ENIGMA are to discover factors that help and harm the brain; the sheer size of the dataset is unprecedented, making it possible to see which effects on the brain are robust and consistent by pooling data worldwide. The idea for ENIGMA originated in late 2009 and the consortium has since published some of the largest brain imaging studies in the world—both in terms of the total number of individuals genotyped and scanned (now over 33,000) and in terms of the number of scientists collaborating [several hundred co-authors, in Stein et al. (2012), Thompson et al. (2014), and Hibar et al. (2015)]. Also, by pooling brain imaging and genomic data from tens of thousands of people, we were able to overcome several technical and sociological barriers; here

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we outline some of the strategies employed and the main findings and lessons learned. As befits a chapter in a book on brain connectivity, we also summarize the tactics that ENIGMA is beginning to employ to discover genetic influences on brain connectivity.

## Genetic Influences on the Brain

By 2009, nearly 100 studies had been published showing that numerous measures of brain structure are *heritable* (Blokland et al. 2012). In other words, individual differences in our genetic code do affect specific features of the brain, such as the overall volume of the brain, the size of the hippocampus, and even measures of functional activity based on EEG or functional MRI. To establish this, researchers began by studying family-based cohorts or twins who were scanned with anatomical or functional MRI; when people with greater genetic similarity were compared, their brains were found to be more similar, on average, than were unrelated people of the same age and sex.

To formalize these ideas, the *classical twin design* has often been used to estimate the heritability of a behavioral trait by studying both identical and fraternal twins (siblings or other family members are often evaluated as well; Boomsma et al. 2002). Based on structural equation models, or even based on simpler approaches involving correlations, twin studies are able to estimate what fraction of the observed variability in a brain measure is due to genetics, that is, due to the genetic differences among individuals. Many measures of brain structure, such as the total amount of gray or white matter in the brain or the overall volume of the ventricles, were found to be heritable; that is to say, genetic factors are involved in determining their eventual values. Note that this type of genetic analysis does not require the direct examination of the DNA sequence, only the study of resemblances among family members with different degrees of familial relatedness (e.g., identical twins, siblings, etc.).

Soon afterwards, 3D “maps” of heritability began to be produced for a variety of brain measures, such as regional gray matter volumes in the cortex (Thompson et al. 2001), cortical thickness (Joshi et al. 2012), surface area (Chen et al. 2012), and fiber microstructure in diffusion-weighted MRI scans (Chiang et al. 2009). The proportion of variance due to genetic factors is not expected to be completely uniform across the brain. In general, genetic variation accounts for around half of the observed variance for many brain measures, in some cases more, making neuroimaging measures an attractive target for in-depth genetic analysis (Glahn et al. 2007).

The high heritability of brain structure is in line with many behavioral genetic studies showing substantial genetic effects on behavior and even risk for neurological and psychiatric illnesses, such as Alzheimer’s disease and schizophrenia. Genetic studies have shown that numerous traits relating to personality, cognition, and even risk for neurological or psychiatric disease are influenced by genetics to some degree. The influence of genetic versus environmental factors on cognition

and intellectual performance was one of the most hotly debated scientific topics of the twentieth century (Jensen 1969; Lewontin et al. 1984). Of course, even if we concede that genes play some role in behavior, several caveats to heritability calculations apply: genetic variants do not influence the brain independently of other factors, and their effects may depend on a person's age, sex, level of nutrition, education, or many other contextual factors in the population (Visscher et al. 2008). Although they are not necessarily heritable, epigenetic factors, such as methylation and acetylation, act on the genome to switch off or promote the action of certain parts of our genetic code. Also, an individual's environment may be correlated to some degree with their genotype; for example, people with a natural aptitude for certain kinds of activity may seek out environments that promote those activities. This makes the effects of genes and environment difficult or impossible to disentangle. Gene x Environment interactions are also found, where a gene's effect on the brain or behavior is accentuated or suppressed under certain conditions. In fact, much work in the fields of pharmacogenomics and personalized medicine depends on the notion that people with certain genetic risk factors may be less or more responsive to medication or other kinds of therapy. As such, the quest to identify genetic variants that relate to brain measures is likely to accelerate our genetic understanding of brain disease and mental illness. With this in mind, ENIGMA has several projects that relate brain measures to genomic variation and to disease, a topic that we will return to later.

## Finding the Genes Involved

Knowing that a brain measure is heritable—or influenced by genetic factors—is the first step on the long road towards identifying *specific* differences in the genome that influence it. By 2009, genetic “sequencing” had become relatively inexpensive, and it was possible to reliably identify a person's individual DNA sequence at each of over one million genetic locations, based on a person's blood or saliva sample. Although well over 99 % of the genetic code is identical across healthy individuals, people do differ substantially in specific areas of the genetic code: there are deletions, expansions, and even single-nucleotide or single “letter” spelling differences in the base pair sequence. Some of these genetic differences do not affect the protein product, if the gene is expressed at all. Other genetic differences render the protein product dysfunctional or modify its activity, and they may influence brain function and behavior and our risk for disease.

Genotyping companies began to offer genotyping services whereby over a million common genetic variants—or single nucleotide polymorphisms (SNPs)—could be assessed cheaply; in the United States, for example, some personalized genomics companies offered to send a person a million “letters,” or nucleotides, of their genetic code for \$99 (in U.S. dollars). This ability to genotype common variants in the genome led to a surge in the popularity of genome-wide association studies (GWAS), efforts to identify markers or common variants in the human

genome that are statistically associated with a certain trait, such as obesity, schizophrenia, depression, or Alzheimer's disease. Many of these genomic screens were very successful. For instance, certain "risk genes," such as *APOE*, *CLU*, and *TREM2*, have alternative sequences wherein one form is more commonly found in patients with Alzheimer's disease (Harold et al. 2009; Jonsson et al. 2013). The quest to find these risk-associated genetic variants is motivated by finding new drug targets or, in the short term, evaluating a person's risk for a specific disease, which can help in clinical trial design.

Again, several caveats apply. Common variants are not the only source of genetic variations that have an impact on the brain; in fact, rare variants—or even *private* variants found only within a single family or individual—have been found that associate with risk for autism or other disorders (Sanders et al. 2012; Purcell et al. 2014). When GWAS was first feasible on a large scale, studies of tens of thousands of individuals began to unearth common genetic differences associated with cholesterol levels in the blood and with bone density, obesity, or stroke, and a range of other common conditions. In each study, the genome was scanned for sequence variations associated with a single trait, such as a person's height, body mass index, or a psychiatric diagnosis such as schizophrenia or bipolar illness, for example. Because of the high risk of false positives—searching millions of letters of the genetic code would likely detect many false associations—geneticists began to enforce a very high statistical threshold to implicate a genetic variant in a disorder, often requiring tens of thousands of subjects to find an association and replicate it.

## GWAS of the Brain

Around 2009, GWAS began to be performed on brain measures [see supplementary information in Medland et al. (2014)], such as temporal lobe volume (Stein et al. 2010). Although some of the top "hits" in these studies seemed convincing from a mechanistic point of view, many geneticists argued that the power to detect common genetic variants that affect the brain was very limited, even in samples of approximately 1000 subjects. As brain imaging data are expensive and time-consuming to collect, only the largest national initiatives could even achieve sample sizes of 1000 subjects; the Alzheimer's Disease Neuroimaging Initiative (ADNI; Jack et al. 2008), for example, was one of the largest studies ever attempted with neuroimaging. ADNI still took many years to recruit and scan a cohort of 800 people at 58 sites across North America. Power calculations suggest that cohorts of 10,000 or more subjects should be needed to zero in on genomic regions with reliable associations to brain measures, unless of course their effect sizes are extremely large. And so began a debate as to whether imaging would offer a more efficient way to detect influential genetic variants.

## Counterarguments and Power

Two arguments were commonly advanced to suggest that large samples might not be required for successful genetic studies of brain images, but the evidence for each argument began to wane. The first was that some image-derived measures might be more highly reproducible than psychiatric diagnostic tests or cognitive scores; some measures from images (such as the density of connections between brain regions) might be closer to the biology of the gene action as well and therefore show a stronger effect. For example, a growth factor gene, such as *BDNF*, might influence the cell numbers or cell volumes in a specific structure of the brain, such as the hippocampus. If so, then the statistical association between common variants influencing the function of that gene and the size of the brain structure should be fairly easy to identify in a database of brain scans. As we shall see, this optimism had to be tempered; at least for the brain measures assessed so far, sample sizes needed for successful genetic association studies have been about the same as those needed to discover risk genes for clinical conditions such as Alzheimer's disease or schizophrenia, though less than those for major depression, and have been on the order of tens of thousands. Even so, one should bear in mind that the large samples required to detect effects does not mean effects are trivial or unimportant. Rare variants with large effect, for example *TREM2*, appear to double a person's risk for Alzheimer's disease (Guerreiro et al. 2013; Jonsson et al. 2013) and cause brain tissue loss at twice the normal rate (Rajagopalan et al. 2013). Despite the fact that only 1 % of people carry this risk allele, the aggregate effect on society is no doubt substantial, perhaps similar to other mental disorders with similar prevalence but with devastating impact.

A second argument was that we should focus on candidate genes when looking for factors that affect the brain, rather than performing a completely open-ended, genome-wide search. Because certain growth factors in the brain—*BDNF*, and *NGF*, for example—have polymorphic variants within their genes, they could be natural candidates for affecting volumes of the brain and perhaps other more subtle features of brain function, such as functional activation or metabolism. Except for major risk genes such as *APOE*, a risk factor for late-onset Alzheimer's disease, ENIGMA's data would ultimately show that many of these candidate genes, long thought to affect brain measures, did not appear to do so in much larger sample sizes. This finding was confirmed in samples of 10,000 brain scans or more, samples large enough to detect effects accounting for as little as 1 % of the variance in a brain measure.

Between 2009 and 2012, over 20 cohorts worldwide came together to form ENIGMA. The initial study (called "ENIGMA1"; Stein et al. 2012) found common variants near the *TESC* gene that were associated with hippocampal volume measured in MRI scans of the brain. The SNPs involved also affected gene expression in living brain tissue, as confirmed by analysis of post-mortem brain tissue. Carrying one form of the gene was associated with a hippocampal volume that was smaller by an amount equivalent to about 3 years of brain aging, a small

but substantial effect on a brain scan; the possible cognitive effects of this genetic change, and their effects on disease risk, are now the target of study. Other findings of ENIGMA1 included an association between intracranial volume in healthy subjects and a genetic variant in *HMGA2*, a gene that had formerly been associated with height and whose role in cell proliferation was beginning to be understood. ENIGMA would not have been able to demonstrate that these associations were robust without the help of another large consortium, CHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology), whose GWAS studies of the aging brain in five large elderly cohorts were crucial in establishing the generality of the findings. In fact, when the two consortia exchanged their top findings for genetic variants associated with hippocampal and intracranial volumes, their top five hits were the same. The most associated SNPs in each consortium were the same ones, even though the studies assessed different individuals and were designed independently (Bis et al. 2012).

## Non-biological Information Arising from ENIGMA

After ENIGMA's first study, some hypotheses had to be revised about which genes might affect brain measures and how easy it would be to detect their effects. Some of the "hallowed" candidate genes in psychiatric genetics—*COMT*, for example—were initially hailed as explaining a fair proportion of the risk for psychiatric illness, only to be found less relevant or not well supported in follow-up studies [see Button et al. (2013) for an analysis of this "winner's curse" effect]. Perhaps for the same reasons, many genes expected to influence brain structure were not found to do so, even in ENIGMA's highly powered study. Only *APOE* had a convincing effect on hippocampal volume, with many growth factors and common psychiatric risk genes not showing demonstrable effects in much larger sample sizes than previously studied. Although it is not possible to rule out an effect that is undetected, the effects of these genes would likely be less than 1 % of the measured variance, much smaller than some originally thought.

On the bright side, the power to replicate findings across the whole diverse range of cohorts and populations in ENIGMA was surprising and encouraging. Most studies contributing to ENIGMA were designed with other goals in mind, on different scanners and some on different continents. As the data were pooled after the fact, substantial work went into showing that reproducible and accurate measures could be made of the same brain regions across sites and scanners [see Supplemental Materials in Stein et al. (2012)]. On the genomic side, ENIGMA's use of reference panels such as HapMap3 and the 1000 Genomes datasets to "impute" genetic data collected from different genotyping chips also made it possible to pool data across sites, attaining a power not previously imagined for a brain imaging study.

## But Do the ENIGMA Genes Affect Disease Risk?

Shortly after the initial study was published, a second initiative was started to screen the genome for common variants associated with volumes of seven other subcortical structures (the project was called “ENIGMA2”; Hibar et al. 2015) and 34 other cortical structures (ENIGMA3; in progress). In the course of these studies, a collaborative partnership began with the Psychiatric Genomics Consortium (PGC) to see if any of the brain-relevant genes were “enriched” in the PGC’s own screens for genes associated with psychiatric illnesses such as schizophrenia. ENIGMA studies of schizophrenia, epilepsy, obsessive compulsive disorder, and Alzheimer’s disease are currently underway. There is some optimism that these enrichment analyses may show that some of the same genes that affect the structure of the brain also create risk for disease. Several disease risk genes are known to be convincingly associated with brain differences: many of the top 20 or so Alzheimer’s risk genes (according to [alzgene.org](http://alzgene.org)) are associated with differences in brain structure, metabolism, or pathology identifiable with brain imaging. Some of the logistics involved in looking up ENIGMA’s genes in other psychiatric GWAS involves performing “checksum” tests to exclude people who have taken part in both GWAS studies; such participants could cause spurious associations, making it important to screen out non-independent data.

In parallel, ENIGMA launched several working groups to identify brain measures that showed the greatest patient vs. control differences in cohorts of patients with schizophrenia (Turner et al. 2014; van Erp et al. 2015), bipolar illness (Hibar et al. 2014), depression (Schmaal et al. 2014, 2015), and ADHD (Hoogman et al. 2014). Some of these studies now number 4000–8000 subjects, making them the largest studies ever of their respective disorders. Clearly, the power to identify correlates of behavioral and cognitive dysfunction, and relevant modulators of illness such as medication effects, makes these efforts highly informative. All these studies are in their earlier phases now, but ultimately they may yield new sources of information to distinguish psychiatric profiles based on brain imaging and genetics and for differential diagnosis and even perhaps prognosis.

## Searching Brain Images for Statistical Effects

In brain imaging studies more generally, it is common to align a group of subjects’ images to a standardized coordinate space and try to find parts of the brain with consistent activations or brain regions whose activity relates to modifiable parameters of the experimental design. One such approach, called *statistical parametric mapping*, or SPM, can identify brain regions where brain signals relate to some external predictor, such as a task performed in the scanner, or psychiatric diagnosis. To do this, often a regression model is fitted at thousands to millions of different

locations in a 3D brain image and the significant regions are shown, after some suitable correction for the multiple statistical tests made in the image.

## Brain-Wide Genome-Wide Scanning

Although it may seem a daunting task, Stein et al. (2010) proposed a method to screen every voxel (location) in the brain and every genotyped variant in a genomic screen to search both images and genomes at once for promising associations. The sheer number of computations can exceed one billion statistical tests. The first such efforts found no genuinely replicated associations and were computationally feasible only on a massively parallel computer cluster.

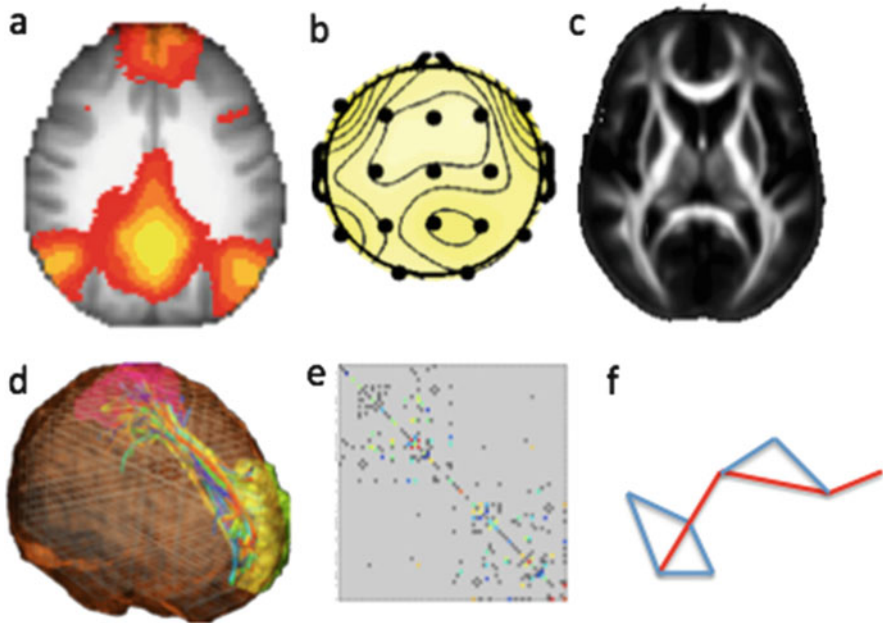
Due to the massive number of statistical tests, the significance threshold that needs to be achieved to control for false positives is around a billion to one (see Medland et al. 2014). Even so, this threshold was achievable and far exceeded by several “hits” (i.e., genetic associations) in ENIGMA2, making the approach feasible statistically as well. Although voxel-wise GWAS is a tour de force computationally, it can be combined with other techniques for dimension reduction to focus the search on promising signals. These methods can be statistical, based on genetic clustering or prioritizing brain measures with highest heritability, or they can be based on biology and known genetic pathways. Such efforts are reviewed in Thompson et al. (2013, 2014, 2015).

## Genetic Screening of the Connectome

Based on the power that has been achieved so far through ENIGMA to discover common genetic influences on brain structure, it should now be clear that genome-wide analysis can also be extended to measures beyond that of individual neuro-anatomical structures to discover factors that influence how regions of the brain are connected or work together, i.e., measures of brain connectivity. Brain connectivity can be modeled in terms of networks describing how different regions of the brain function together (functional connectivity) or how they are physically connected in terms of the strength, integrity, or pattern of the white matter fibers (structural connectivity) (Fig. 1).

Family and twin studies found that specific connections and global organizational measures are heritable in both functional and structural networks. Glahn et al. (2010) found that the resting state functional network, derived from blood oxygen level-dependent functional MRI imaging, is remarkably heritable; Smit et al. (2010) used EEG-based measures of connectivity to study the heritability of measures of network “clustering” and path length. Fornito et al. (2011) examined local and global measures of efficiency and connection distance, along with overall density for resting state networks. In a similar investigation of functional





**Fig. 1** Various forms of connectivity measures extracted from brain images; all these methods allow us to study the brain from a higher dimensional perspective and observe correlations and connections between regions. In the more classical approaches, voxelwise maps of activity or DTI-based integrity measures can be mapped out. In addition to MRI-based imaging, electrodes can be placed around the brain to obtain functional activation or electrophysiological signals. Structural or functional connections between different regions can be estimated. A broad search over all possible connections can lead to mapping the information in a matrix to form a mathematical graph representation. Global properties of this matrix can then be thought of as measures that describe the network as a whole. For example, one measure of interest examines the shortest path lengths in the network or the paths with the lowest numbers of connections between one region, or node, and all the others

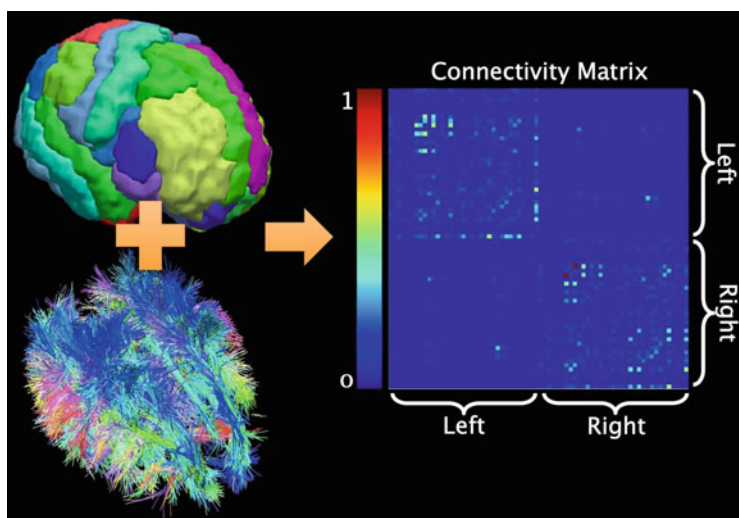
connectivity in children, however, van den Heuvel et al. (2013) did not detect significant heritability for certain local measures while robustly finding that more global measures of network organization were heritable. Structural connectivity and patterns of organization are also influenced by genetic factors. Jahanshad et al. (2013b) showed that a fraction of the total number of detected connections are indeed highly heritable, while Bohlken et al. (2014) studied the network's topology to establish heritability for other global measures of fiber connections.

The genetic influences on these brain measures have also been established by exploring the effect of known disease risk genes on the connectome. Candidate gene analyses have even suggested that connectome properties may be associated with genetic risk factors for diseases and disorders such as autism (Scott-Van Zeeland et al. 2010; Dennis et al. 2011), schizophrenia (Braskie et al. 2012), and dementia (Brown et al. 2011; Jahanshad et al. 2012); given the history of candidate gene associations in psychiatric genetics, these findings will need to be replicated

and assessed in larger samples. There is clear potential for using connectivity measures as targets for genetic analysis or perhaps even for successfully discovering disease risk genes through a genome-wide search.

While functional connectivity measures also appear to be promising targets for genetic study, here we focus our discussion on expanding structural connectivity analyses for large-scale genetic analyses in ENIGMA. Figure 2 shows the structural connectivity matrix from an individual: it stores information on the proportion of detected fibers connecting each pair of brain regions. Jahanshad et al. (2013a, b) proposed a method to map structural connectivity based on diffusion-weighted MRI and prioritize the resulting connections for a genome-wide screen to identify common variants that affect brain connectivity. Not all possible connections are found in all individuals and not all parts of the brain are directly connected to all the others, so the connectivity matrices are relatively sparse (see Fig. 2). As such, a matrix that represents some measure of the quality or density of connections between all pairs of regions on the cortex may represent a number of possible connections that is equal to the square of the number of regions, in theory. For example, breaking up the cortex into 70 regions (Desikan et al. 2006) would lead to a connectivity matrix of almost 5000 elements, but only around 1 % of these might show high reproducibility and heritability in a population.

Using a classical twin model based on identical and fraternal twins, Jahanshad et al. (2013a, b) identified the heritable connections within structural connectivity



**Fig. 2** The structural connectivity matrix. Using standard anatomical MRI and a variant called diffusion-weighted MRI for fiber tracking, we can map out the structural connectivity network of the brain. To do this, we combine a cortical parcellation (*top left*) with a set of fiber pathways computed using tractography algorithms (*bottom left*). The resulting connections between all pairs of cortical regions are organized into a connectivity matrix (*right*). Its rows and columns correspond to the cortical regions and the magnitudes of the elements represent properties of the connections detected between them, such as fiber integrity or density

matrices of several thousand elements and carried forward only the approximately 50 heritable connections into a genome-wide screen. The gene showing a genome-wide and connectome-wide level association with a particular connection within the connectome, *SPONI*, was subsequently also associated with cognitive decline in an independent study, albeit at a different locus (Sherva et al. 2014). This gene is also implicated in amyloid processing (Hafez et al. 2012), a key component of Alzheimer's disease pathology.

Clearly, the ability to pursue such an approach on a large scale, within ENIGMA, depends on several factors: a working group, ENIGMA-DTI, was set up to assess its feasibility. First, unless diffusion-weighted MRI measures show greater genetic effect sizes than other traits assessed so far, there must be tens of thousands of DTI scans available from people with GWAS for such a study to be well powered. Second, the format of the connectivity matrix must be sufficiently standardized and agreed on in advance, to allow the exchange and pooling of brain connectivity data across sites.

Encouragingly, by mid-2014, the ENIGMA-DTI working group had amassed around 10,000 DTI scans. Pilot studies showed that the data could be analyzed in a consistent way (Jahanshad et al. 2013a; Kochunov et al. 2014). As the ENIGMA3 project involves a cortical volumetric analysis, the current plan is for ENIGMA to use those cortical regions as the basis for a structural connectivity analysis, using the same voxel-wise analysis of the connections as advocated in Stein et al. (2010) and Jahanshad et al. (2013b). It will be interesting to see if similar sample sizes, tens of thousands, are needed to find and replicate genetic associations with measures of structural brain connectivity. It could be that mathematical tactics for dimension reduction, or network-based measures, are also attractive targets for genetic analysis; so far the relative merits of each of these measures remains to be seen.

## Caveats for Multi-site Genomic Analysis of the Connectome

In addition to the caveats noted for pooling multi-site structural MRI data, several additional caveats make the analysis of connectivity challenging. First, the choice of tractography methods can result in different matrices; the method only detects fibers that the algorithm can identify, so many true connections may be missed and some "false positive" connections will also be detected. As with standard MRI, these factors are largely influenced by the signal to noise ratio and resolutions of the images. Often, an arbitrary threshold is implemented to remove the false positive connections, but short fibers can be filtered out. If a connection appears to be weak or inconsistent across subjects, this connection may also be removed. Interestingly, Fornito et al. (2011) found that, for resting state networks at different thresholds, the degree of heritability varied for different global measures, and heritability was not uniform across all nodes; there were various levels of genetic influence for each measure. Lastly, while seemingly intuitive, the results do depend on the parcellation of the cortex, the way the cortical surface is split up into regions of

interest. Depending on the goals of the study, parcellation schemes can be improved to maximize power.

Before embarking on large-scale collaborative efforts combining connectivity matrices and network metrics, confounding factors such as these should be properly investigated as is currently being done in ENIGMA's working groups, such as the ENIGMA-DTI and EEG working groups, among others. For example, in single site studies, Buchanan et al. (2014) performed test-retest reliability analyses to explore the reliability of measures after exploring a variety of commonly used approaches. Dennis et al. (2012) and Zhan et al. (2013) explored the consequences of altering the thresholds used to define networks as well as different methods of tractography, respectively.

## Future Directions: Adaptive Connectomics and EPIC

In Prasad et al. (2014), we introduced a method called "EPIC" (Evolving Partitions in Connectomics) to compute brain connectivity in such a way as to be optimally sensitive to statistical effects in a population, such as the effect of Alzheimer's disease or depression. Clearly, the brain can be divided into regions in many different ways, such as spectral clustering (Craddock et al. 2012), hierarchical clustering (Blumensath et al. 2013), or even genetic clustering (Chen et al. 2012). Each one leads to a different definition of brain connectivity between the resulting regions. Although the set of possible partitions is truly astronomical in number, EPIC offers a principled approach to identify the optimal set of brain regions to find specific statistical effects on the connectivity of the resulting regions. Put another way, if we are seeking brain regions whose connectivity is disrupted in Alzheimer's disease, the algorithm will merge and split parts of the brain until it reaches a set of connections that best differentiates Alzheimer's disease patients from controls.

With this adaptive method in mind, it is easy to see how the brain could be partitioned in such a way to maximize the heritability of the connections, automatically de-selecting unfavorable measures before performing a genome-wide screen. If that were done, genomic screens of the connectome might be more efficient, allowing a two-way interplay between discovered genes and the search for connections they might affect.

Still further potential is available once a genome-wide hit is detected; in that case, it should be possible to merge and split cortical sectors so that the genetic effect of a SNP or set of SNPs is more powerfully detected. In other words, one could adjust the cortical partition to maximize the proportion of variance that can be attributed to SNPs or common genetic variants. These high-dimensional searches of the connectome and genome at once will draw upon the full breadth of ingenuity of mathematicians and geneticists alike.

With the scale of ENIGMA and other consortia now planned, it seems likely that we may crack the "Enigma code" of the brain's connectivity network, using intelligent algorithms and the concerted efforts of the worldwide scientific

community. Identifying the genetic influences on the structure and function of the human brain can allow us to understand what makes us human and help uncover the mechanisms causing psychiatric illness.

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