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# Brain imaging genomics: influences of genomic variability on the structure and function of the human brain

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**Abstract:** Brain imaging genomics is an emerging discipline in which genomic and brain imaging data are integrated in order to elucidate the molecular mechanisms that underly brain phenotypes and diseases, including neuropsychiatric disorders. As with all genetic analyses of complex traits and diseases, brain imaging genomics has evolved from small, individual candidate gene investigations towards large, collaborative genome-wide association studies. Recent investigations, mostly population-based, have studied well-powered cohorts comprising tens of thousands of individuals and identified multiple robust associations of single-nucleotide polymorphisms and copy number variants with structural and functional brain phenotypes. Such systematic genomic screens of millions of genetic variants have generated initial insights into the genetic architecture of brain phenotypes and demonstrated that their etiology is polygenic in nature, involving multiple common variants with small effect sizes and rare variants with larger effect sizes. Ongoing international collaborative initiatives are now working to obtain a more complete picture of the underlying biology. As in other complex phenotypes, novel approaches – such as gene–gene interaction, gene–environment interaction, and epigenetic analyses – are being implemented in order to investigate their contribution to the observed phenotypic variability. An important consideration for future research will be the translation of brain imaging genomics findings into clinical practice.

**Keywords:** brain phenotype, genetics, SNP, CNV, MRI, genetic variation, GWAS

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## Introduction

The past 15 years have witnessed unprecedented advances in the acquisition of brain imaging and genomics data. Brain imaging genomics is a rapidly evolving research field that combines data obtained through: (1) analyses of genetic variation, such as single-nucleotide polymorphisms (SNPs), copy number variations (CNVs), and epigenetic information; and (2) different brain imaging methods, usually magnetic resonance imaging (MRI). The major aim is to provide insights into the genetic architecture of biological pathways that influence normal and disturbed brain structure and function. This information may facilitate understanding of the functioning of the human brain. For brain disorders such as neuropsychiatric and neurological disorders, this knowledge may improve diagnostic and prognostic assessments and help to identify molecules that can be targeted by novel therapies.

Data are obtained via a broad range of imaging methods available that provide data on brain structure and function. In principle, these methods can be subdivided into those that generate data on brain structure and those that measure brain function. For brain structure, widely applied assessment methods include structural MRI and diffusion-tensor imaging. Brain function, such as resting-state activity, can be measured using functional MRI, while monitoring of the action of molecules within the brain is frequently performed via positron emission tomography (PET) using receptor binding ligands and single-photon emission computed tomography [1]. Collectively, these structural and/or functional measures are termed brain imaging phenotypes.

Progress in genomic methodology has paved the way for important advances in brain research. In particular, improved knowledge of the human genome and inter-individual genomic variation has made genome-wide association studies (GWAS) possible [2], and next-generation sequencing technologies have enabled rare variant analyses.

As for genetic analyses of other complex phenotypes and disorders, brain imaging genomics has evolved from single-variant candidate gene analyses in relatively small samples to large GWAS performed by international, collaborative research consortia comprising tens of thousands of individuals, mostly drawn from the general population. There are several reasons why there has been a focus on population-based cohorts rather than patients. In many psychiatric diseases, e. g., schizophrenia, pathological processes appear to occur already in early brain development and can be superimposed by disease- or therapy-related epiphenomena later in life. In neurodegenerative diseases, e. g., Alzheimer's disease, brains can be strongly altered at the time of diagnosis as a result of secondary effects. Therefore, it may be difficult to distinguish causal from secondary effects using brain imaging genomics in patients.

In contrast, brain imaging genomics studies in population-based individuals offer the advantage that the identification of causal molecular processes involved in basic structural and functional brain phenotypes (such as cortical thickness [CT] or resting-state activity) can be identified without disease-related epiphenomena. In addition, a better understanding of the genetic factors influencing normal brain function may provide important insights into processes underlying brain dysfunction as their contribution to disease etiology can be subsequently tested in GWAS results of different neuropsychiatric, neurological, or neurodegenerative disorders.

The present review discusses key findings in brain imaging genomics, the advantages and limitations of the various approaches, and planned future directions in the field.

## Heritability estimates for brain imaging phenotypes

Brain measures derived via noninvasive scans reveal substantial structural variation in subcortical brain regions. Researchers have long assumed that genetic factors contribute to the observed phenotypic variation. Formal genetic studies, in particular twin studies, have played an important role in estimating the proportion of variance that is attributable to genetic and environmental factors, respectively. Here, a quantitative imaging trait is considered to be influenced by genetic factors if the correlation is higher in monozygotic than in dizygotic twins, and decreases with greater genetic distance. These studies have demonstrated that a substantial proportion of the observed variation in brain imaging phenotypes is influenced by genetic factors [3–6]. Although heritability estimates for all subcortical regions are high, regional variation is evident. Moderate to strong heritability has also been demonstrated for other neuroimaging-derived measures, such as subcortical shape [7] or connectivity [8]. These brain imaging phenotypes can be used in genetic association studies. They represent endophenotypes, which may be associated with behavioral traits in healthy individuals or clinical symptoms in patients with neuropsychiatric disorders.

## Candidate gene studies

The aim of early brain imaging genetics studies was to identify associations between brain phenotypes and single genetic variants in candidate genes (for a review, see [9]). Researchers hypothesized that the various functions of these genes, which range from neural growth and survival to signal transduction, were implicated in the manifestation of diverse brain phenotypes. Well-known candidate genes include the genes encoding brain-derived neurotrophic factor (*BDNF*), catechol-O-methyltransferase (*COMT*), and the serotonin transporter (*SLC6A4*). These three genes have undergone extensive investigation in imaging genetics studies, as well as in case-control studies of diverse psychiatric disorders, including schizophrenia, bipolar disorder, and major depressive disorder (e. g., [10]). Key criticisms of these early studies were that: (1) they were insufficiently powered; and (2) they often generated false-positive results and unreplicable large effect sizes that appeared to represent winner's curse effects. Furthermore, larger, negative studies often remained unpublished, which created a "publication bias" [11]. The inconsistency of small candidate gene studies was demonstrated retrospectively by large meta-analyses [12]. Furthermore, extensive methodological heterogeneity has hampered cross-study comparisons.

These early studies demonstrated that larger samples would be necessary to generate the statistical power required to disentangle the genetic architecture of brain phenotypes. The subsequent establishment of large-scale, in-

ternational consortia, such as ENIGMA, has indeed led to major breakthroughs [13].

## Genome-wide association studies

In response to the success achieved by large-scale research collaborations for other genetically complex diseases and traits, the brain imaging genomics field is now increasing its use of the GWAS approach. The first large GWAS in the field was performed in 2012 by the ENIGMA consortium [14]. This aimed to identify genetic variants with an influence on the volume of the hippocampus, a brain structure of key importance in terms of learning, memory, and stress regulation and which is implicated in numerous neuropsychiatric disorders. The study also investigated total brain volume and intracranial volume. The discovery sample comprised data from approximately 7,800 subjects, including healthy individuals and patients with neuropsychiatric disorders. An intergenic SNP (rs7294919) in chromosomal region 12q24.22, which regulates the expression of the gene *TESC*, was associated with hippocampal volume and decreased hippocampal volume by 1.2 % per risk allele. Another variant (rs10784502), located within the gene *HMGA2*, was associated with intracranial volume (decreased the volume by 0.58 % per risk allele). A key conclusion of this study was that contrary to previous hypotheses, the genetic architecture of brain imaging endophenotypes might be comparable to that of other complex traits, rather than being influenced by common variants with larger effect sizes. Biological insights into the brain phenotypes of interest were limited. However, this initial study encouraged researchers to pursue the GWAS approach and extend their collaborations in order to optimize sample sizes.

A larger follow-up study of hippocampal volume in 33,000 individuals confirmed the previously identified SNP locus on 12q24.22, and identified novel associations, some of which concerned genes involved in oxidative stress and neurogenesis [15]. The same study applied linkage disequilibrium (LD) score regression to estimate the SNP heritability of hippocampal volume and found that a substantial proportion (approximately 18 %) of the variance in hippocampal volume could be explained by common genetic variation. For the phenotype intracranial volume, a follow-up study in 37,000 individuals also identified novel loci, which were enriched near genes involved in growth pathways [16].

In subsequent studies, the analyses have been extended to other brain structures through the application of continuously improving statistical and bioinformatic methods. The ENIGMA2 consortium conducted a GWAS of intracranial volume and the volumes of seven subcortical regions (nucleus accumbens, caudate, putamen, pallidum, amygdala, hippocampus, and thalamus) in 30,700 individuals from 50 cohorts [17]. The study identified five novel genetic variants with an influence on putamen and caudate nucleus volume. The strongest effects were found for the putamen, whose volume was associated with a novel intergenic locus (rs945270, 0.52 % variance explained). The study generated evidence that this locus alters the expression of the gene *KTN1* in both blood and brain tissue [17]. Variants with an influence on putamen volume clustered near developmental genes that regulate apoptosis, axon guidance, and vesicle transport. This study also addressed the question whether a genetic covariance exists between structural brain phenotypes and the risk of psychiatric disorders. For this purpose, the authors tested SNPs with a genome-wide significant association to diverse neuropsychiatric disorders. However, none of these SNPs showed a pronounced influence on subcortical volumes.

The most recent GWAS of subcortical brain structures was a meta-analysis of data from the ENIGMA and CHARGE consortia and the UK Biobank, which was performed in 2019 and combined data from more than 38,800 individuals [6]. A total of 48 genome-wide significant loci were identified that were related to the volumes of the nucleus accumbens, amygdala, brainstem, caudate nucleus, globus pallidus, putamen, and thalamus (Figure 1). Careful annotation of these loci using data on methylation, gene expression, and neuropathology revealed that 199 genes had a putative involvement in neurodevelopment, synaptic signaling, axonal transport, apoptosis, and inflammation/infection. These genes were significantly enriched for *Drosophila* orthologs that show an association with neurodevelopmental (neuroanatomy-defective) phenotypes in flies, suggesting evolutionarily conserved mechanisms [6].

Moreover, the neurodevelopmental genes included the brainstem-associated *PTPN1*. Interestingly, it can be transcriptionally regulated by MECP2, mutations in which cause Rett syndrome, a progressive neurological developmental disease affecting brain stem function. Of note, pharmacological inhibition of PTPN1 in a mouse model suggested a therapeutic approach for Rett syndrome [18].

The aim of a very recent ENIGMA study was to identify genetic factors with an influence on human cortical surface area (SA) and CT [19]. Previous research has demonstrated phenotypic variation in SA and CT, and has shown

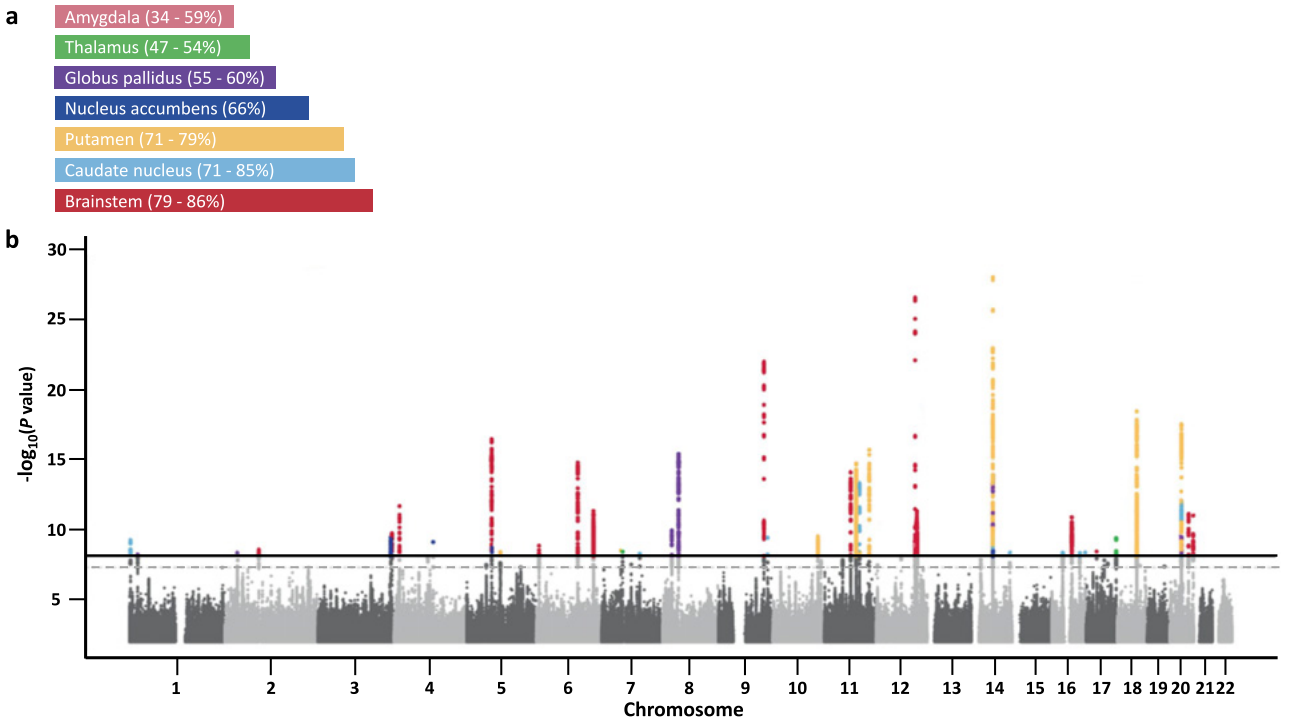


**Figure 1:** (a) Range of family-based heritability estimates for brain volume in seven subcortical brain regions and (b) Manhattan plot of GWAS results for regional volumes in more than 38,800 individuals [6]. Associations with regional volume were found for a total of 48 genome-wide significant loci. Each region is assigned a specific color which corresponds to that of the associated SNPs. The dashed horizontal line indicates the threshold of genome-wide significance ($P < 5 \times 10^{-8}$) and the solid horizontal line indicates this threshold after an additional Bonferroni correction for the independent phenotypes.

that this variation is associated with neurological, psychological, and behavioral traits. However, our current understanding of the impact of genetic variation on cortical size and patterning is limited to rare, highly penetrant variants in model organisms [20, 21]. These variants often disrupt cortical development and lead to a pronounced alteration in postnatal brain structure. At writing, few data are available concerning the influence of common genetic variation on these cortical structures. To address this issue, Grasby et al. conducted a GWAS of brain MRI data from more than 51,000 individuals across 60 research sites [19]. A total of 241 and 14 genome-wide significant and replicated loci influencing SA and CT, respectively, were identified. Common genetic variants explained 34 % and 26 % in total SA and average CT, respectively. Further bioinformatic analyses demonstrated that variation in SA was influenced by genetic variants that alter gene regulatory activity in neural progenitor cells during fetal development. In contrast, CT was influenced by genetic variation in active regulatory elements in the adult brain, which may reflect processes that commence in the later stages of fetal development, such as myelination, branching, or pruning [19].

There is accumulating evidence that the "brain age gap," i. e., the difference between an individual's predicted age based on MRI and the chronological age, is increased in several common brain disorders, sensitive to clinical and cognitive phenotypes and genetically influenced. In a recent study, machine learning algorithms were used to estimate the age of individuals using structural MRI data [22]. Differences between predicted and chronological age were then calculated to form individual-specific scores. These were then introduced to a GWAS with discovery and replication steps using 16,834 individuals from the UK Biobank and other cohorts. Two genome-wide significant SNPs were found; one mapped to the potassium channel gene *KCNK2* and correlated with sulcal width, while the other tagged a DNA inversion called H2 and was correlated with reduced white matter SA. *KCNK2* encodes a potassium channel that is predominantly expressed in the central nervous system [23]. Studies in mouse models suggested that the channel is involved in cerebral ischemia [24], dysfunction of the blood–brain barrier [25], and neuroinflammation [26].

To date, GWAS in brain imaging genomics have led to breakthroughs that are comparable with those achieved

for psychiatric disorders, namely, the statistically robust identification of associations between common genetic variations and different brain structural phenotypes. Contrary to expectations at the initiation of brain imaging studies 20 years ago, the genetic architecture and the genetic nature of the associated variants do not differ substantially from those of complex diseases. However, previous authors have suggested that brain imaging phenotypes may show a lower degree of polygenicity [27] and that these phenotypes are more directly influenced by underlying genetic factors than is the case for psychiatric disorders. Investigation of these phenotypes in healthy individuals may provide important insights into normal brain functioning. Beyond this, a plausible hypothesis is that brain imaging phenotypes may also influence disease susceptibility across multiple psychiatric disorders and that pleiotropic effects of genetic variants might thus be mediated by influencing underlying brain imaging phenotypes. Brain imaging genomic investigations in healthy individuals and patients with psychiatric disorders may shed light on these issues, and complement genomic studies of psychiatric disorders.

As in neuropsychiatric genomics, an important aim of brain imaging genomics is the identification of the biological pathways that underlie the phenotype of interest. These two fields encounter the same challenges. For example, many associated variants are not yet functionally annotated and are often located in noncoding regions of the genome. However, as for psychiatric disorders, an understanding of the biological pathways that are implicated in brain imaging phenotypes is of major importance. Important aims of future research will be to annotate the function of these variants and, in parallel, to further increase the power of GWAS via increased sample sizes. This will implicate further genetic variants and generate a more refined picture of the implicated biological pathways. At writing, most studies are confined to participants of European ancestry. To enable the identification of novel associations and the validation of existing associations, studies in other ethnicities are clearly warranted.

## Polygenicity and genetic overlap of neuropsychiatric disorders and brain imaging phenotypes

Recent GWAS of diverse psychiatric disorders have identified a large number of significantly associated SNP variants (see the review articles of affective disorders and schizophrenia in this issue), each of which has relatively small genetic effects. The emerging picture is that psychiatric disorders have a polygenic and heterogeneous genetic architecture. GWAS of subcortical brain structures and cortical SA have also revealed many trait-associated SNPs, and it is becoming evident that these traits are also polygenic in nature, although the extent of this might be less than that predicted for psychiatric disorders [27]. Through the availability of large, well-powered GWAS data sets for psychiatric disorders and MRI-based brain phenotypes, genomic approaches that exploit this polygenic nature can now be used to evaluate the genetic overlap between these traits. In fact, many differences in brain structure and function have been reported between patients with psychiatric disorders and controls, e. g., case-control differences of subcortical volumes have been reported for schizophrenia [28] and bipolar disorder [29]. The finding of a significant overlap between psychiatric disorders and brain imaging phenotypes would shed light on the respective primary disease processes. Franke et al. [30] investigated this question using: (1) GWAS data from the Psychiatric Genomics Consortium (PGC) schizophrenia group; and (2) GWAS data from the ENIGMA consortium on the volumes of eight brain structure (nucleus accumbens, amygdala, caudate nucleus, hippocampus, pallidum, putamen, thalamus, and intracranial volume). The authors evaluated the overlap of common genetic variation at the levels of: (1) overall genetic architecture (using LD score regression [31]); and (2) individual genetic variants. The study found no significant evidence for an overlap (pleiotropy) between common genetic variation that predisposes to schizophrenia and common genetic variation with an influence on any of the eight brain structures of interest. Therefore, the volumetric differences observed in patients with schizophrenia may either be epiphenomena or may be influenced by other genetic factors than the ones impacting on volumetric differences in healthy individuals.

Other studies, e. g., the ENIGMA2 investigation [17], have also tested for a genetic overlap and generated similar results. However, the picture is not entirely consistent. Lee et al. used partitioning-based heritability analysis [32] – a method which estimates the variance explained by all the SNPs in a specific functional or organizational category, e. g., on a chromosome – and found an overlap between variants associated with schizophrenia and eight brain structural phenotypes [33]. The authors also tested GWAS data for other psychiatric disorders and found an overlap between specific brain volumetric measures and autism spectrum disorders, major depressive disorder, and bipolar disorder.

Another approach that is becoming increasingly popular in terms of addressing the polygenic nature of complex brain phenotypes and testing the effects of combinations of risk variants on brain phenotypes in individual subjects is the calculation of polygenic risk scores (PRS; see also the review in this issue). These scores represent a weighted sum of associated variants, and can be employed to investigate the effects of various burdens of risk alleles, e. g., those derived from GWAS of neuropsychiatric disorders, on brain phenotypes. For these studies, both very large collaborative data sets and smaller, phenotypically well-characterized, population-based and clinical samples are required.

However, since psychiatric disorders and the drugs used to treat them can have influences on brain imaging phenotypes, PRS studies should ideally investigate effects in both healthy controls and patients with psychiatric disorders. As an example, Opel and colleagues investigated the effects of a PRS for the personality trait neuroticism on cortical brain structure in healthy individuals and patients with major depressive disorder [34]. They showed that the polygenic score for neuroticism was associated with a decreased cortical SA of the inferior parietal cortex and the precuneus in both healthy controls and patients with major depressive disorder. As reduced SA in the inferior parietal lobe has previously been reported as a feature of adolescent major depressive disorder [35], the findings suggest that genetically determined cortical surface reductions in neuroticism might reflect an increased risk of developing major depressive disorder [34].

Overall, the PRS approach has substantial potential in terms of translation of genetic findings into clinical practice [36–39]. Currently available evidence suggests that the genetic overlap between brain structure and psychiatric disorders is not particularly pronounced. However, in the future, more powerful studies may reveal effects that are too weak for detection using current approaches.

## Copy number variation

In a small percentage of patients with a neuropsychiatric disorder, in particular those with schizophrenia or autism spectrum disorders, single CNVs (either a deletion or a duplication of a particular genomic region) in their genomes are probably the strongest contributory factors in terms of disease pathogenesis. These CNVs may provide a starting point for investigations into the mechanisms that underlie brain function and dysfunction. Brain imaging genomics studies have therefore been initiated to elucidate the relationships between CNVs and imaging phenotypes. While these disease-associated CNVs have strong genetic effect sizes, they are not fully penetrant. This offers the opportunity to pursue separate investigations of their effects on brain imaging phenotypes (and also behavior) separate from those of manifest disease. In a population-based sample from Iceland, carriers of CNVs that were predisposed to schizophrenia and/or autism spectrum disorders and who had no history of a psychotic or autism spectrum disorder were tested for cognitive abnormalities and brain structural changes [40]. The results demonstrated that for some of the investigated CNVs, the cognitive abilities of carriers were between those of population-based controls (without a CNV) and patients with schizophrenia. This suggests that rather than being "nonpenetrant" in carriers with no psychiatric diagnosis, these CNVs showed reduced expressivity. The study also demonstrated that carriers of a deletion at 15q11.2 had a reduced gray matter volume in the perigenual anterior cingulate cortex and the left insula. Both regions had been identified as structurally altered regions in a previous meta-analysis of first-episode psychosis [41].

Other recent studies investigated subcortical brain volumes in individuals carrying one of two CNVs on 16p11.2. One CNV is located proximally and the other distally. Both CNVs can occur as either a deletion or a duplication, and predispose carriers to autism spectrum disorders and schizophrenia (see the review article on schizophrenia in this issue). The proximal CNV was found to modulate brain networks associated with well-replicated structural brain abnormalities seen in patients with schizophrenia and autism spectrum disorders [42]. For the distal 16p11.2 CNV, Sonderby et al. [43] identified 12 deletion carriers and 12 duplication carriers. The authors then compared the brain imaging data of these 24 subjects with those of more than 6,800 noncarriers. The authors found associations between the CNV and specific brain structures. In particular, negative dose–response associations with copy number were found for intracranial volume and the volumes of the caudate, pallidum, and putamen.

The results of these studies indicate that the investigations of CNVs – particularly in individuals with no diagnosis of neuropsychiatric disorder – can provide key insights into the affected brain structures and functions. It is these perturbed brain structures and functions that may eventually lead – in combination with additional genetic and environmental factors – to overt disease. Given the low population allele frequency of these CNVs, the major challenge for future studies will be the recruitment of sufficiently large samples of CNV carrier samples. This can only be achieved via very large population-based studies (e. g.,

UK Biobank) or by international collaborations. Initiatives of this nature are currently ongoing, and will shed light on the effects of other disease-associated CNVs.

## Gene–environment interactions, epistasis, and epigenetics

Brain imaging genomics studies are currently investigating how the interaction between genetic variation and environment (GxE) influences brain structure and function in relation to neuropsychiatric disorders [44]. This is of major interest in terms of future clinical practice, since emerging evidence suggests that exposure to specific environmental factors may result in effects such as an altered response to treatment. Brain imaging genomics is well suited to the identification of such interactions, an advance that could lead to altered or new therapeutic treatments and the identification of at-risk individuals who may benefit from earlier interventions. Two limitations of many GxE studies to date have been low statistical power and a lack of replication [45]. Furthermore, the focus on single candidate gene–environment interactions may oversimplify the "genetic reality," since each of the tested variants makes only a minimal contribution to disease risk. To address these aspects in a more systematic manner, GxE studies must be conducted at the genome-wide level and take sets of risk variants into account. This in turn would require the availability of very large data sets, which will only be feasible through large-scale collaborations.

Studies of gene–gene interactions are similarly challenging. As is true for other complex traits and diseases, gene–gene interactions might account for a proportion of the hidden heritability. Such studies involve a high multiple testing penalty. However, the power of GWAS in brain imaging genomics is now increasing via the enlargement of consortia and biobanks, and thus large-scale epistatic studies may soon become feasible. These would help define the genetic variance that underlies brain structure and function [11].

Another emerging topic of interest in brain imaging genomics is epigenomics. The investigation of DNA methylation, a process which is modulated by both genetic factors and environmental exposures, may facilitate the discovery of novel biomarkers for disease-related brain phenotypes. These studies currently rely on blood DNA methylation as a proxy. In a very recent epigenome-wide association study by the ENIGMA epigenetics working group [46], hippocampus, thalamus, and nucleus accumbens volumes were investigated in more than 3,300 individuals. No significant associations were found with the volumes of the thalamus or the nucleus accumbens. However, differentially methylated regions were found to be associated with hippocampal volume. Brain imaging epigenomics is a promising field, and may be particularly useful in terms of: (1) understanding the impact of the environment on the epigenome; and (2) the performance of longitudinal studies of healthy, at-risk, and affected individuals [39]. Nonetheless, current substantial limitations to this approach include disparities between the methylation states of blood, saliva, and brain tissue, as well as the methodological challenges involved in harmonizing data across independent data sets.

## Ongoing work and future directions

Over the past 15 years, the field of brain imaging genomics has made substantial progress. Large, international, collaborative studies have overcome the initial lack of reproducible findings, and will be a key component of future work. As is the case for many other complex phenotypes and neuropsychiatric disorders, currently available findings explain only a fraction of the heritability of each brain phenotype. Larger studies in diverse population groups/ethnicities will be required in order to obtain a more complete picture of: (1) the underlying common and rare genetic variation; and (2) the influence of this variation on biological pathways and molecular mechanisms, including gene–environment and gene–gene interactions and epigenetic mechanisms. To interpret the region-specific effects of brain phenotype-associated genetic variation, more comprehensive and detailed transcriptomic and epigenomic maps of the brain will be needed. This is currently being addressed by the Allen Institute [47], researchers from the EU-flagship Human Brain Project [48], and other research groups worldwide.

To increase the power of imaging genomics studies and explain more of the variance in findings, increasing consideration is being given to multimodal and multivariate approaches [49]. However, these require even greater computing capacities and more stringent statistical corrections. Methods are also being developed to reduce the dimensionality of the data sets, e. g., using machine learning methods. Despite these advances, replication studies will remain the most reliable method in terms of reducing false-positive associations.

As in psychiatric disorders, next-generation sequencing-based approaches (exome or genome sequencing) will be used to study the effects of rare variation on

brain phenotypes and to refine established brain phenotype–gene associations.

Brain imaging genomics and genomic studies in psychiatric disorders offer significant synergy and can make a large clinical impact. These complementary approaches will likely improve our understanding of the molecular mechanisms implicated in the pathways that determine both normal brain function and dysfunction, which leads to various brain disorders. Ultimately, this could eventually lead to the identification of biological markers. This in turn will allow more refined diagnostic assessment and provide more effective and precise pharmacological targets [50].

## Conclusions for research and clinical practice

- Brain imaging genomics combines analyses of genomic data and brain phenotype data. It aims at the identification of the molecular processes that influence normal and disturbed brain structure and function.
- Large GWAS of brain structural phenotypes have identified common variation which explains a substantial proportion of the phenotypic variance and have demonstrated that the etiology of brain structural phenotypes is polygenic in nature.
- Studies that evaluated the overlap of common genetic variation between different neuropsychiatric disorders and brain structural phenotypes found no clear evidence for pleiotropic effects. Therefore, the volumetric differences observed in patients (e. g., with schizophrenia) may be epiphenomena, which are unrelated to the primary genetic causes of the disease. Alternatively, they may be influenced by other genetic factors than the ones impacting volumetric differences in healthy individuals.
- Particular CNVs, which predispose to autism spectrum disorders and schizophrenia, were demonstrated to have an effect on brain structure and cognitive abilities of healthy carriers. These studies can generate key insights into brain structures and functions affected by disease-associated CNVs.
- As in other complex phenotypes, novel methodological approaches (investigation of the effects of rare genetic variation, gene–gene and gene–environment interactions, and epigenetics) are being implemented in order to investigate their contributions to structural and functional brain phenotypes.
- Brain imaging genomics is likely to improve our understanding of the molecular mechanisms that determine normal and disturbed brain function. This could ultimately lead to the identification of biological markers for more refined diagnostic assessment, change people's lifestyles, and provide more effective and precise pharmacological targets.

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