

[For consideration as part of the ENIGMA Special Issue]

**Ten years of Enhancing Neuro-Imaging Genetics through Meta-Analysis:**

**An overview from the ENIGMA Genetics Working Group**

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## Abstract

Here we review the motivation for creating the ENIGMA (Enhancing NeuroImaging Genetics through Meta Analysis) Consortium and the genetic analyses undertaken by the consortium so far. We discuss the methodological challenges, findings and future directions of the Genetics Working Group. A major goal of the working group is tackling the reproducibility crisis affecting ‘candidate gene’ and genome-wide association analyses in neuroimaging. To address this, we developed harmonised analytic methods, and support their use in coordinated analyses across sites worldwide, which also makes it possible to understand heterogeneity in results across sites. These efforts have resulted in the identification of hundreds of common genomic loci robustly associated with brain structure. We showed common and distinct genetic loci to be associated with different brain structures, as well as genetic correlations with psychiatric and neurological diseases.

**Why did we build the ENIGMA consortium?** The consortium was formed in 2009, largely in response to the growing evidence of a lack of reproducibility dubbed “the replication crisis” in imaging genetics. At this time, the first major works of the Psychiatric Genomics Consortium were being presented at conferences (Neale et al., 2010; The Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium, 2011a, 2011b), and we had observed the improvement in statistical power and increase in reproducibility that could be achieved through large-scale meta-analysis. In late 2009, we were beginning to see a series of genome-wide association (GWAS) publications using phenotypes derived from magnetic resonance imaging (MRI) attempting to answer complex and important questions in psychiatry and neurology. At that time, it was common to see GWAS papers reporting not only main effect analyses but also interactions with diagnosis or putative risk variables in sample sizes of less than 1,000 people. Insufficient power and sample size remain ongoing issues within the field, as recently highlighted by Szucs and Ioannidis (2019) who examined the sample size of clinical and experimental MRI studies published in 2017 and 2018 in four prominent neuro-imaging journals and found that still less than 5% of these studies had sample sizes larger than (Szucs & Ioannidis, 2019).

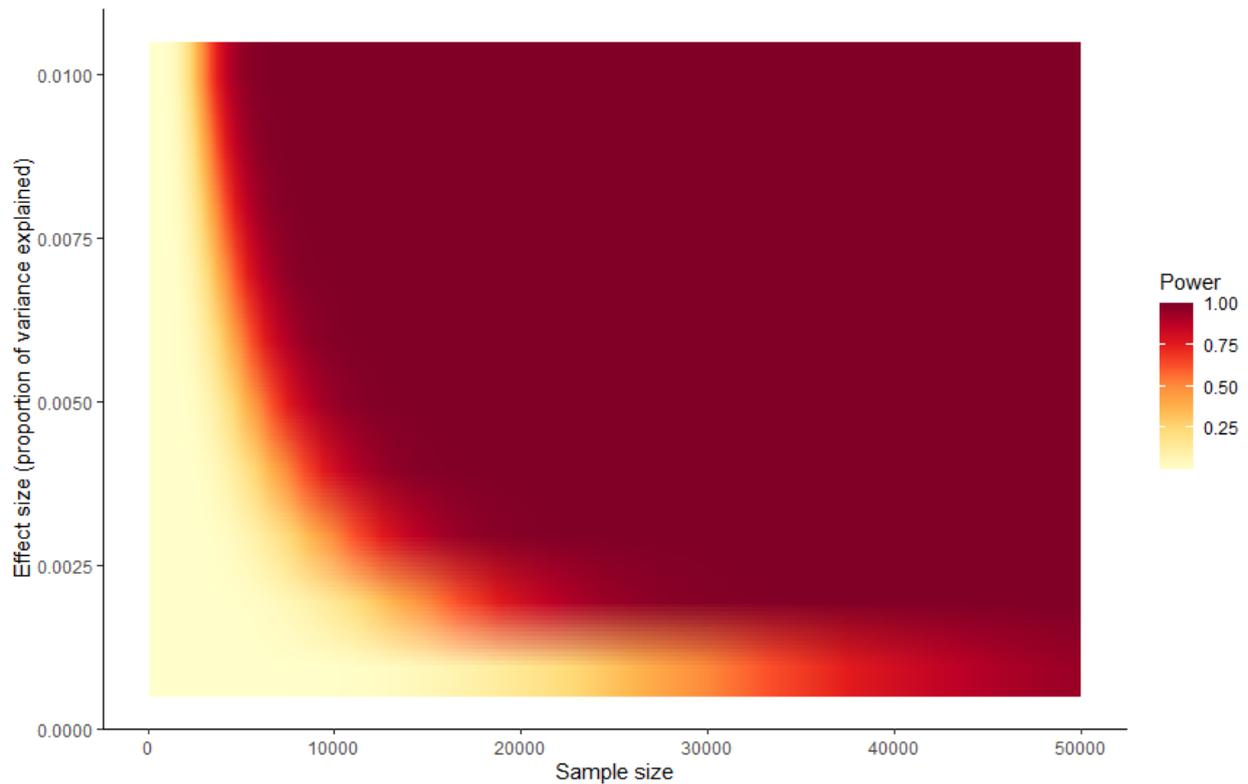
In response to these issues, Thompson and Martin sent an email to neuro-imaging groups around the world asking for interest in being part of a collaborative meta-analysis consortium focusing on imaging genetics. The key points in this email were that, although every group would understandably want to publish its own paper reporting their own findings, (1) the power calculations do not change just because the phenotype acquisition is expensive, (2) it was likely that the individual studies would not be large enough to find significant genetic effects, and (3) even if they did, it would still be necessary to replicate these findings in independent samples. From these beginnings, the ENIGMA consortium now involves more than 2,000 scientists from over 400 institutions in more than 40 countries (Thompson et al., 2020). While our initial focus was on GWAS and genetic analysis of imaging data, this quickly broadened, with the development of a series of clinical and methods Working Groups focusing on answering important questions around the impact of disorders and diseases on brain structure and function for which more power was also required to obtain more robust results.

**What were our major methodological challenges?** We knew one of the first methodological challenges we would face would be addressing heterogeneity and the perceived insurmountable problems arising from heterogeneity in scanner performance and imaging protocols across groups. We addressed these issues by making a conscious decision to conduct meta- rather than mega-analyses, which allowed the site level analyses to be run by those who knew the phenotypic data best. This also ensured that the analyses controlled for scanner and protocol effects where necessary and enabled an evaluation of heterogeneity across sites at the individual genetic variant level. By conducting analyses at the collection sites rather than bringing all imaging data to one central location for analysis, we were able not only to address site-level heterogeneity but also ensure that

contributing groups were able to quality control, process, impute and analyse their own genotypic data, with technical and scientific support provided where necessary. This helped to disseminate these skills within the imaging community and at the same time maximized participation by avoiding challenges related to data sharing.

The second major methodological issue we encountered was the treatment of multiple testing and decisions regarding phenotype selection. Working in imaging genetics, we not only had to consider the multiple testing correction related to the number and the correlation structure of phenotypes being tested, but also those relating to the number of genetic variants being analysed, while accounting for the autocorrelation patterns within the genome due to linkage disequilibrium. Moreover, we had to consider how to reconcile the two different approaches to multiple testing adopted within the fields of imaging (which typically adopts a false discovery rate approach) and genetics (which typically uses Bonferroni corrections). GWAS analyses currently analyse around 10,000,000 variants across the genome, and these analyses are often conducted for a large number of phenotypes. As the downstream interpretation of GWAS results often uses the P values from the GWAS as input, we elected to adopt a Bonferroni approach to multiple testing correction and used spectral decomposition analysis to determine the effective number of independent traits being analysed (Nyholt, 2004).

**What have we done?** Our first major ENIGMA project was published in 2012 and focused on identifying common genetic variants associated with hippocampal and intracranial volumes. These analyses brought together data from 22 cohorts and led to a combined sample size of 21,000 individuals (Stein et al., 2012). In addition to identifying genome-wide significant loci influencing hippocampal volume and intracranial volume, these analyses confirmed that - except for a signal for *APOE* in a cohort that included individuals with Alzheimer's disease - there were no other significant results at the individual cohort level; there were also no cohort-level significant results when the analyses were restricted to individuals without a neurological or psychiatric diagnosis. Thus, by bringing together the data from these 22 cohorts, the 206 co-authors on this paper worked together to ensure that the resulting analysis would be well powered and robust, rather than 22 underpowered 'null result' papers. Another important finding from this paper was that the distribution of effect sizes seen on these imaging phenotypes was very similar to that which had been observed for other physiological traits in humans; with individual common genetic variants typically explaining less than 1% of the variance in the trait. As shown in **Figure 1**, large sample sizes are needed to robustly detect genetic variants with realistic effect sizes using conventional genome-wide significance thresholds; however, due largely to budgetary constraints, many individual studies have been designed to detect effects in the >5% range (similar to the effect sizes seen for *APOE* in Alzheimer's disease). Ongoing work by multiple groups is focusing on increasing power using multivariate tests (e.g. van der Meer et al., 2020), Bayesian priors, and other conditional analyses (e.g. Smeland et al., 2018). However, as the central hypothesis of most GWAS and the bioinformatic and functional follow up of findings are essentially univariate in nature, well-powered univariate analyses supported by replication and meta-analyses remain crucial.

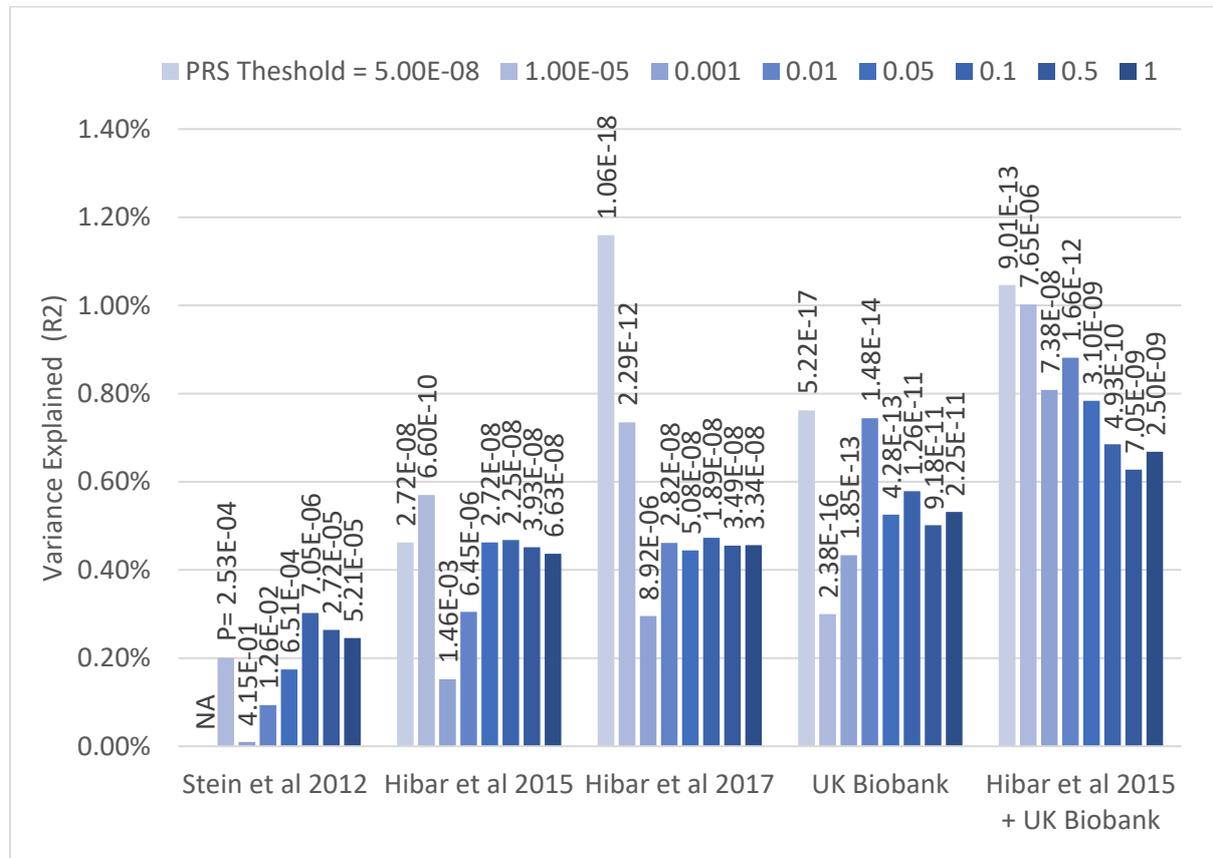


**Figure 1.** Power to detect a genome-wide significant locus (at  $\alpha=5*10^{-8}$ ) for variants explaining 0.1 to 1.0% of the variance in a quantitative trait, for sample sizes of 100 to 50,000 individuals. These analyses assume that the data come from unrelated individuals, and that additional covariates in the GWAS are not correlated with the trait. See <https://github.com/kaustubhad/gwas-power> for R code and a tutorial on calculating power for GWAS; see also Smith and Nichols (2018), who discuss power in the context of testing multiple traits.

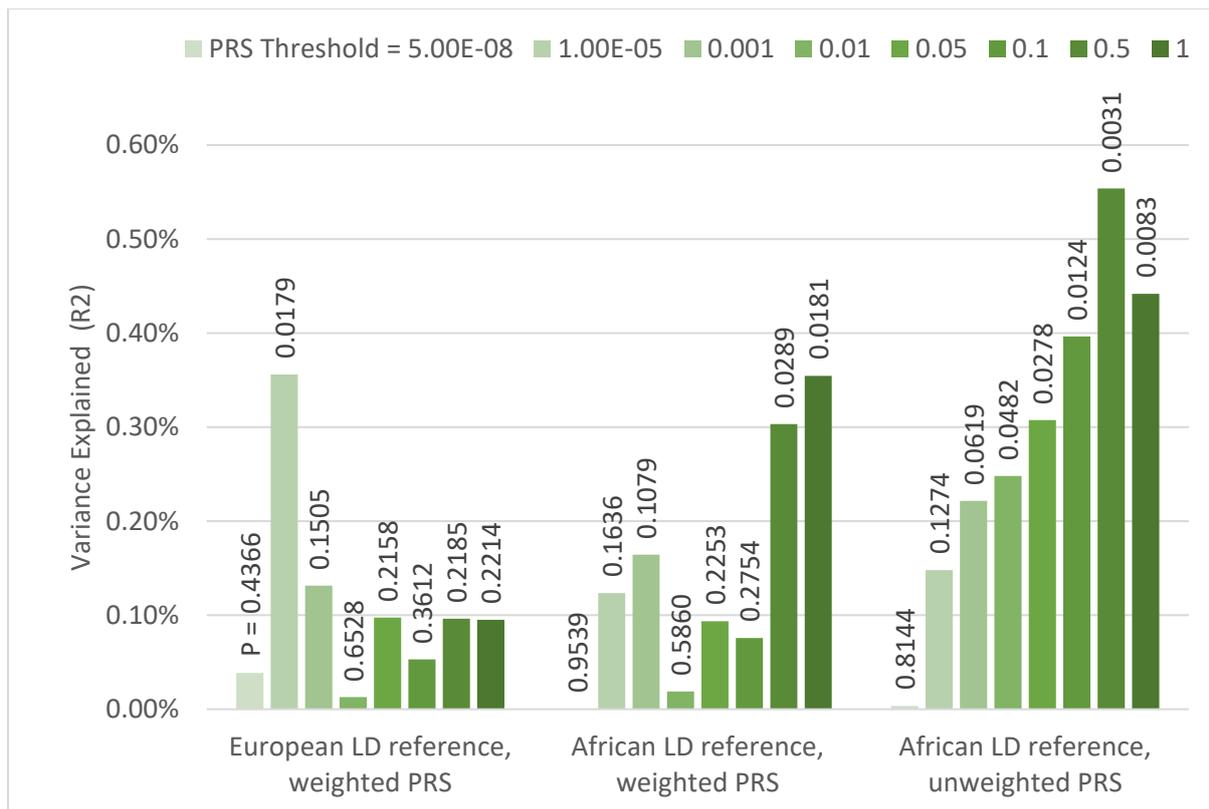
The second major ENIGMA GWAS paper focused on a wider range of subcortical volumes as well as intracranial volume (Hibar et al., 2015). These analyses included contributions from 30,717 individuals from 50 different cohorts and identified numerous common genetic variants influencing subcortical structures. Most variants identified in these analyses influenced specific structures; however, this may to some extent be due to the way in which imaging data are analysed and the corrections for total or intracranial volume when analysing substructures. Despite this, at a genomic level, the results for the individual substructures clustered by developmental and functional subdivisions.

In addition, we were able to demonstrate that subcortical volumes were significantly influenced by common variants with SNP based heritabilities derived from the GWAS results explaining 7 to 15% of the phenotypic variance. Since the publication of these analyses in 2015, we have worked with our collaborators in the CHARGE consortium to publish a series of updates with increased sample sizes on common genetic variants influencing hippocampal, intracranial, and other subcortical volumes; these results now account for 15 to 30% of the phenotypic variance in these structures (Adams et al., 2016; Hibar et al., 2017; Satizabal et al., 2019). Similarly, as shown in **Figure 2**, even when predicting into paediatric samples (aged 9-11), the performance of polygenic risk scores (PRS), derived from meta-analyses of participants across the lifespan, has increased as the power of the GWAS have increased. However, most work in this field has focused on analysis of data from participants of European ancestry - which dramatically reduces the accuracy of polygenic prediction in non-European samples because of differing patterns of LD and allelic effects across ancestries. Notably, as shown in **Figure 3** this reduction is somewhat ameliorated through the use of unweighted polygenic scores. Focusing on

increasing sample size of non-European ancestry samples to improve the weights used in polygenic risk score calculation is likely to be the best method of increasing the predictive power in these populations.



**Figure 2 Improvement in the polygenic score prediction of hippocampal volume, as power in the discovery GWAS increases.** PRS may be thought of as weighted-sum scores that summarise the results of the GWAS to a given level of significance. PRS analyses were conducted using 4000 randomly selected unrelated participants of European ancestry from the ABCD study, which was not included in the discovery meta-analyses (Casey et al., 2018) (relatedness  $<.025$ ; ancestry defined as  $< 6$  sd from the European reference centroid in a multidimensional scaling analysis). PRS were calculated using the traditional clumping and thresholding approach (`--clump-r2 0.1 --clump-kb 1000`). Weights for these polygenic scores were derived from GWAS for hippocampal volume controlling for ICV from Stein et al 2012, Hibar et al 2015 and 2017, a GWAS of 20,112 UK Biobank participants of European Ancestry, and a meta-analysis of the results from Hibar et al 2015 and the UK Biobank GWAS of 20,111 individuals. Analyses included Age, Sex, ancestry corrections component 1-4 and ICV as covariates.

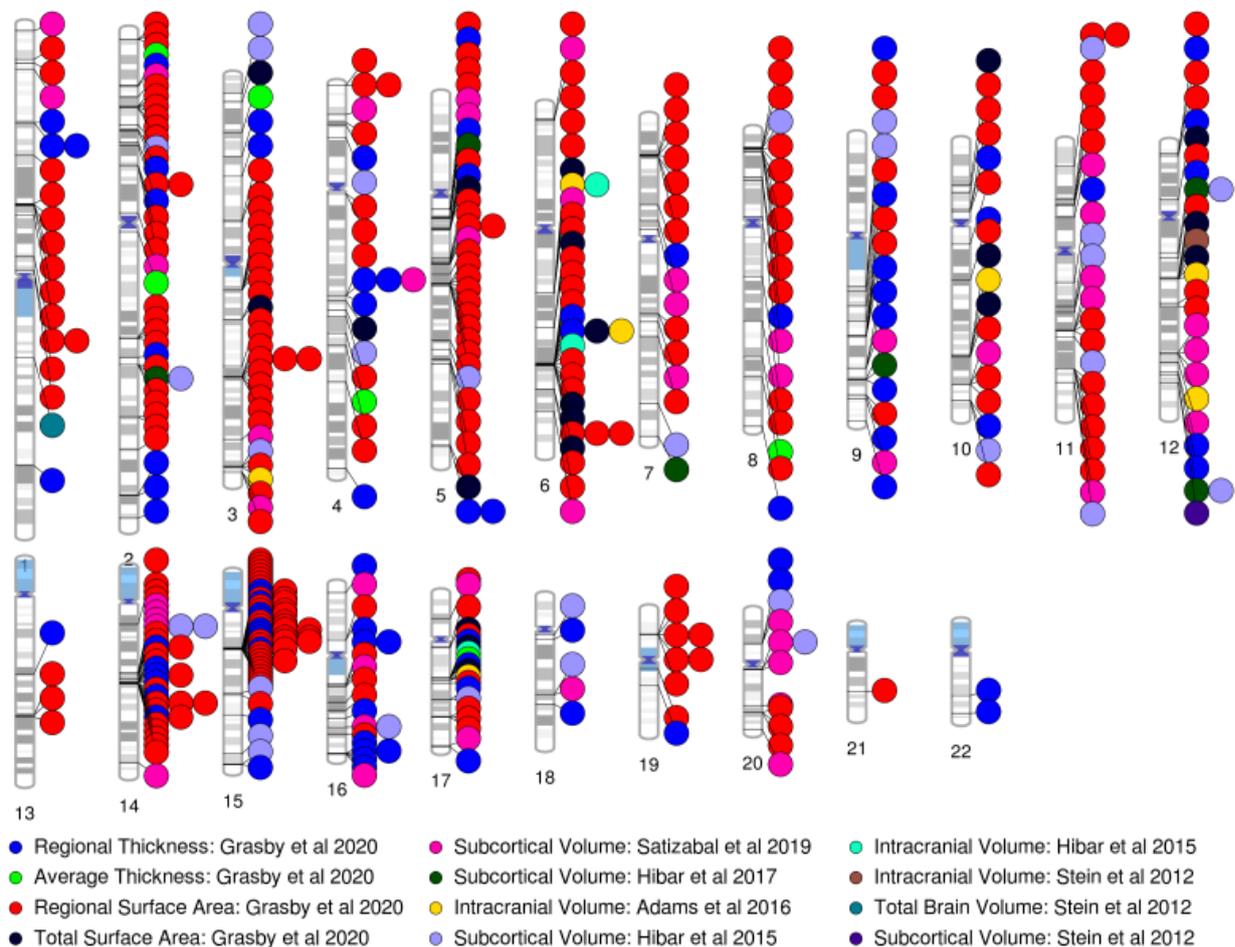


**Figure 3 Performance of cross-ancestry polygenic score prediction as a function of LD reference data and weighting.** PRS analyses were conducted using the 966 unrelated participants of African ancestry from the ABCD study (Casey et al., 2018) (relatedness  $< .025$ ; ancestry defined as  $< 6$  sd from the African reference centroid in a multidimensional scaling analysis). The polygenic scores were derived from a European ancestry meta-analysis of the hippocampal volume GWAS from Hibar et al 2015 and a GWAS of 20,111 individuals from the UK Biobank. PRS were calculated using the traditional clumping and thresholding approach (`--clump-r2 0.1 --clump-kb 1000`) using reference sets of 1,000 participants of European or African ancestry (sampled from the ABCD study). For the weighted PRS, the SNP dosages were multiplied by the betas from the GWAS as is traditionally done. For the unweighted PRS the betas from the GWAS were recoded to 1 if  $\beta > 0$ , -1 if  $\beta < 0$  and 0 if  $\beta = 0$ . Analyses included Age, Sex, ancestry corrections component 1-4 and ICV as covariates.

Our most recent work focused on identifying common genetic variants influencing the surface area and thickness of the cerebral cortex, across all commonly used regions of interest (Grasby et al., 2020). These analyses brought together a discovery sample of over 33,000 individuals from 50 cohorts with a replication sample of around 15,000 individuals. We found enrichment of loci influencing total surface area within regulatory elements active during prenatal cortical development, which supports the radial unit hypothesis (Rakic, 1988). We also found loci impacting regional surface area clustered near genes in *Wnt* signalling pathways known to influence progenitor cell proliferation, surface expansion and areal identity (Harrison-Uy & Pleasure, 2012). Common variants explained 34% (SE = 3%) of the variation in total surface area and 26% (SE = 2%) of variation in average thickness across the cortex, while polygenic risk scores derived from these GWAS analysis explained 2 to 3% of the variance in these traits. We also found genetic correlations (i.e., overlap in genetic effects across traits) between total cortical surface area and cognitive function, Parkinson's disease, insomnia, depression

and ADHD. The degree of genetic overlap with disease risk loci could be visualized for each cortical region, helping to map the relationships between brain structures and these disorders.

Collectively, the work from the ENIGMA Genetics Working Group has identified over 460 genome-wide significant variants influencing the structure of the human brain. As shown in **Figure 4** these variants are located across the genome. In addition to the work of the ENIGMA consortium, the progress in neuroimaging genetics has also been greatly enhanced through meta-analyses conducted by the CHARGE consortium (Adams et al., 2016; Bis et al., 2012; Hibar et al., 2017; Satizabal et al., 2019; Shin et al., 2020; van der Lee et al., 2019; Vojinovic et al., 2018). Similarly, recent analyses from the UK Biobank have allowed further advances in the field to be made (Elliott et al., 2018; Smith et al., 2020; Smith & Nichols, 2018; Zhao et al., 2020) and have facilitated a growing body of work in this area. As the strong SNP-based heritability of MRI-based phenotypes demonstrates, there are still substantially more common variants influencing brain structure yet to be found. As the power of neuroimaging GWAS analyses continues to grow through collaboration and meta-analyses, we can expect to see the number of known loci and the accuracy of polygenic prediction increase markedly.



**Figure 4.** Ideogram summarising the cortical, subcortical and ICV findings from the ENIGMA (Grasby et al., 2020; Hibar et al., 2015; Stein et al., 2012) and ENIGMA-CHARGE (Adams et al., 2016; Hibar et al., 2017; Satizabal et al., 2019) papers.

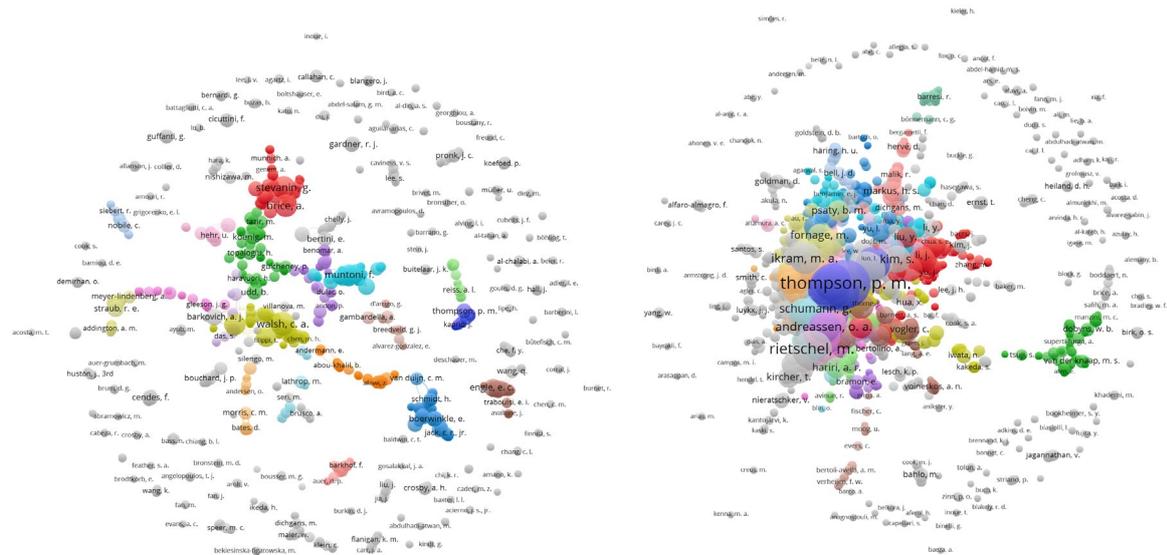
**Where to from here?** As with the vast majority of GWAS, the analytic focus has been strongly centred on single nucleotide polymorphisms located on the autosomes. However, it is important to consider other classes of genetic variants: the ENIGMA CNV working group (see Sonderby et al., 2020, *this issue*) is making important progress in this area. There is also a need to consider the genetic content of the

allosomes or sex chromosomes. Historically, these chromosomes were excluded from GWAS meta-analyses due to a lack of imputation reference data and complications surrounding the modelling of X-chromosome inactivation in females, which is not necessarily complete and may be tissue and timing specific (Tukiainen et al., 2017).

As is the case for many other domains, neuroimaging genetics as a field has typically focused on genotyping cohorts in which MRI data had already been collected. This has led to the majority of analyses focusing on participants of European ancestry. There is a pressing need to address the issue of diversity. Large studies, such as the UK Biobank (Littlejohns et al., 2020) and ABCD (Casey et al., 2018), which have been designed to be more representative of the communities in which the research is being conducted are an important advance in this area. However, more work is needed, and disparities in prediction accuracy cannot be addressed until large-scale genetic studies are undertaken in other ancestral populations.

To provide results with the widest generalizability, our work to date has focused on commonly studied imaging phenotypes derived from cortical and subcortical structures using the most commonly used atlases and parcellation tools. Moving forward, there are obvious avenues for further work comparing results from other atlases and image processing methodologies. Work has also begun on image-wide genome-wide association (Medland, Jahanshad, Neale, & Thompson, 2014), also known as voxelwise GWAS or vGWAS (Hibar et al., 2011; Stein et al., 2010). This approach combines the spatial resolution of brain-wide statistical parametric mapping with the genome-wide search afforded by GWAS. Until recently power was insufficient for simultaneous genome-wide screening of very high dimensional phenotypes, leading to novel strategies for phenotype prioritization and sorting (Jahanshad et al., 2019; Thompson, Ge, Glahn, Jahanshad, & Nichols, 2013). Similarly, there is a need to study other important structural phenotypes such as fractional anisotropy measures derived from diffusion tensor imaging; there is work underway on this within the ENIGMA DTI Working Group (Jahanshad et al., 2013). Beyond brain structure, the genetics of brain activity remains a subject of interest within ENIGMA. This involves ongoing work on (resting state) functional MRI as well as use of other imaging modalities, such as electroencephalography (EEG), where the ENIGMA EEG Working Group has already provided first results (Smit et al., 2018). At the same time, there is also interest in new methods for the analysis of imaging genomics data. Some of these attempt to bring in other sources of bioinformatics data to constrain and guide the search for mechanisms (Shen & Thompson, 2020). A key lesson learned in all these efforts, which will no doubt apply to future machine learning and deep learning efforts in imaging genomics, has been the need for multi-cohort replication in diverse datasets. Multi-site replication can also help address the need to safeguard against false positives arising from too many ‘researcher degrees of freedom’ when many methods and parameters are tried on the same datasets.

Finally, in addition to raising awareness of the importance of conducting well-powered analysis in imaging genetics, ENIGMA has greatly increased the awareness of the need for collaborations among researchers in the field. As shown in **Figure 5a**, from 2000 to 2010, the co-authorship network for published research being conducted in imaging genetics was perhaps best characterized as a sparse network with relatively few connections. However, as shown in **Figure 5b**, since this time, the overall characteristics of the network have largely evolved, and there is now much tighter collaboration among researchers. We look forward to seeing this trend continue as the field of imaging genetics continues to advance.



**Figure 5. Co-authorship network diagrams for imaging genetics publications indexed in PubMed: a) from 2000-2010, and b) from 2010-2020.** Network analyses were conducted using VOSviewer (van Eck & Waltman, 2010) using the default clustering methods, normalised by association strength, using a repulsion strength of 0 in the layout. Data extracted 14/8/2020 using the following search syntax a) (((("2000/01/01"[Date - Publication] : "2010/01/01" [Date - Publication])) AND ((linkage) OR GWAS) AND imaging genetics)) AND MRI) AND English[Language] b) (((("2010/01/01"[Date - Publication] : "2021/01/01" [Date - Publication])) AND ((linkage) OR GWAS) AND imaging genetics)) AND MRI) AND English[Language].

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