

## BRIEF COMMUNICATION

# Distinct genetic basis of common epilepsies and structural magnetic resonance imaging measures

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## Funding information

MING Fund

## Abstract

Focal and generalized epilepsies are associated with robust differences in magnetic resonance imaging (MRI) measures of subcortical structures, gray matter, and white matter. However, it is unknown whether such structural brain differences reflect the cause or consequence of epilepsy or its treatment. Analyses of common genetic variants underlying both common epilepsy risk and variability in structural brain measures can give further insights, as such inherited variants are not influenced by disease or treatment. Here, we performed genetic correlation analyses using data from the largest genome-wide association study (GWAS) on common epilepsy ( $n = 27\,559$  cases and  $42\,436$  controls) and GWASs on MRI measures of white ( $n = 33\,292$ ) or gray matter ( $n = 51\,665$ ). We did not detect any significant genetic correlation between any type of common epilepsy and any of 280 measures of gray matter, white matter, or subcortical structures. These results suggest that there are distinct genetic bases underlying risk of common epilepsy and for structural brain measures. This would imply that the genetic basis of normal structural brain variation is unrelated to that of common epilepsy. Structural changes in epilepsy could rather be the consequence of epilepsy, its comorbidities, or its treatment, offering a cumulative record of disease.

## KEYWORDS

atrophy, brain structure, diffusion tensor imaging, genetics, genome-wide association study, MRI

## 1 | INTRODUCTION

Large-scale collaborative efforts by the ENIGMA-Epilepsy working group have found widespread structural brain differences in people with generalized as well as focal epilepsies, when compared to healthy controls. These

differences often extend considerably beyond any localized epileptogenic focus in the brain.<sup>1,2</sup> Such structural brain differences are thought to underlie various traits like cognitive decline and vulnerability to psychiatric diseases<sup>3</sup> that are frequently comorbid in people with epilepsy. The ENIGMA-Epilepsy studies are based on cross-sectional

See Appendix S3 for a list of members and affiliations of the International League Against Epilepsy Consortium on Complex Epilepsies.

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comparisons of MRI scans between people with epilepsy and healthy controls, which do not allow for inference of causation. Therefore, it is unknown whether such structural brain differences constitute the cause of epilepsy, the result of epileptic seizures, or epiphenomena such as effects of antiepileptic drugs or environmental factors, or some combination of such factors.

Some of these limitations can be overcome by assessing common genetic factors associated with structural brain measurements and genetic factors associated with epilepsy in independent cohorts. Common inherited genetic variants are not determined by disease, treatment, or environmental factors. Susceptibility to epilepsy and variation in structural brain measures are both strongly heritable and largely explained by common genetic variation.<sup>3–5</sup> Recent large-scale efforts have combined genetic and MRI data from tens of thousands of people, to map which genetic variants are associated with structural measures of the brain.<sup>3,5</sup> Combining these data with a large-scale genome-wide association study (GWAS) from the epilepsies<sup>6</sup> represents a unique opportunity to disentangle whether the genetic basis of epilepsy and structural brain variation are shared or distinct.

To do so, we performed genetic correlation analyses to assess whether genetic determinants of structural brain measures are associated with common epilepsy and its main subtypes, focal and generalized epilepsy.

## 2 | MATERIALS AND METHODS

### 2.1 | Study population

The current study is based on summary statistics from the International League Against Epilepsy Consortium on Complex Epilepsies epilepsy GWAS and a combination of structural MRI GWASs from the ENIGMA consortium and the UK Biobank.

The common epilepsy GWAS constitutes a meta-analysis combining 29 different cohorts. After stringent single nucleotide polymorphism (SNP) and sample quality control, approximately 5 million SNPs were assessed in a total of 27 559 people with epilepsy and 42 436 controls in the final meta-analyses.<sup>6</sup> Furthermore, subanalyses were conducted on focal ( $n = 14\,939$  cases) and generalized epilepsy ( $n = 6\,952$  cases). All included subjects were of European ancestry. All analyses were corrected for population stratification using a mixed model association analysis.

We used publicly available summary statistics from the ENIGMA consortium GWAS of 70 measures of gray matter, calculated from genetic data and brain MRI scans in 51 665 individuals of primarily (94%) European ancestry.<sup>3</sup>

These 70 measures consisted of cortical thickness and surface area of 34 brain regions as well as the total surface area and average thickness of the whole cortex. The ENIGMA GWAS constitutes a meta-analysis involving 60 different cohorts, including various population-based cohorts like the UK Biobank as well as case-control cohorts, including a cohort of 178 subjects with epilepsy. Analyses were corrected for age, age-squared ( $\text{age}^2$ ), sex, sex-by-age and  $\text{age}^2$  interactions, ancestry and dummy variables for scanners (if multiple scanners per site were used), and disease status for case-control cohorts. In addition, we used GWAS summary statistics from a study on sulcal morphology in 26 530 individuals of European ancestry from the UK Biobank. This study included 670 measures of regional sulcal width, length, mean depth, and surface area, of which 642 traits with nonzero SNP-based heritability were included in the current analysis.<sup>7</sup>

White matter microstructure GWAS data were obtained from a study that combined genetic data with 110 measures of diffusion-weighted brain MRI scans from the UK Biobank in 34 024 subjects of European (British) ancestry.<sup>5</sup> These 110 measures consist of five diffusion tensor imaging (DTI) parameters (fractional anisotropy, mean diffusivity, axial diffusivity, radial diffusivity, and mode of anisotropy) computed for 21 white matter tracts plus a whole brain average. All analyses were corrected for age,  $\text{age}^2$ , sex, age-sex interaction,  $\text{age}^2$ -sex interaction, imaging site, and population stratification. Similarly, GWAS data using MRI scans of 19 629 subjects of European ancestry from the UK biobank were used to assess genetic contribution to 100 brain volumetric phenotypes, including various subcortical, cortical, and white matter volumes.<sup>8</sup> These analyses were adjusted for age,  $\text{age}^2$ , sex, age-sex interaction,  $\text{age}^2$ -sex interaction, total brain volume, and population stratification.

Total brain volume data were obtained from a GWAS that included 47 316 unrelated subjects of European ancestry.<sup>9</sup> These subjects were derived from a combination of the UK Biobank and the ENIGMA consortium, and all analyses were corrected for population stratification, age, sex, genotype array, assessment center, standing height, and the Townsend deprivation index.

### 2.2 | Genetic correlation analyses

Genetic correlation analyses between common epilepsy and MRI measures of gray and white matter were computed using bivariate linkage disequilibrium score regression (LDSC).<sup>10</sup> Bivariate LDSC utilizes GWAS summary statistics and compares the effect sizes of each SNP, including SNPs that do not reach genome-wide significance, between two traits to assess the overall genetic correlation.

We were not able to exclude any potential sample overlap. However, genetic correlations computed by LDSC are not biased by sample overlap, as sample overlap only affects the intercept of the regression coefficient, but not the slope.<sup>10</sup> Modeling studies confirmed that sample overlap does not lead to biased estimates of genetic correlations.<sup>10</sup> We used default settings of LDSC, with precomputed linkage disequilibrium regression weights from European subjects of the 1000 Genomes project. We computed all genetic correlations analyses separately for all epilepsy combined and its main subtypes focal and generalized epilepsy.

### 2.3 | Power calculations

We used the GCTA-GREML power calculator<sup>11</sup> to estimate the power to detect significant genetic correlations of .05 and .10 or higher (at a type 1 error rate [ $\alpha$ ] of .05) between all epilepsy, focal epilepsy, generalized epilepsy, and each main MRI phenotype of the whole brain. SNP-based heritability for each phenotype was calculated using LDSC<sup>10</sup> and converted to liability scale.<sup>4</sup> For these calculations, we assumed a population prevalence of .005 for all epilepsy, .003 for focal epilepsy, and .002 for generalized epilepsy.<sup>4</sup>

## 3 | RESULTS

We did not find any nominally significant genetic correlation (all  $p > .05$ ) between all epilepsy, focal epilepsy, or generalized epilepsy with average surface area, cortical thickness, brain volume, fractional anisotropy, mean diffusivity, axial diffusivity, radial diffusivity, or mode of anisotropy of the whole brain (Figure 1). Power calculations showed that we had statistical power ranging between

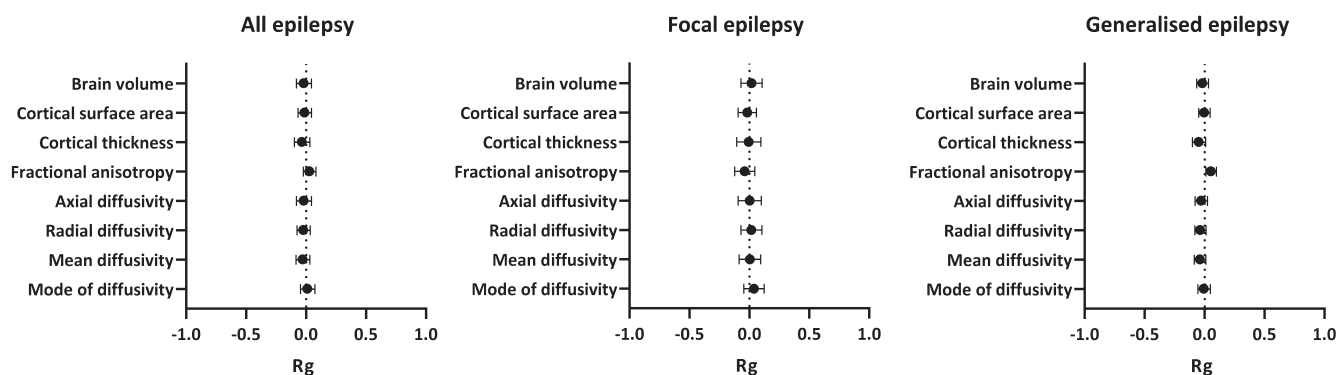
25% and 100% to detect genetic correlations higher than .05 between any of the epilepsy subtypes and any of the MRI phenotypes (Appendix S1). The power to detect genetic correlations higher than .10 ranged between 73% and 100%. For generalized epilepsy (the epilepsy subtype with the highest SNP-based heritability), we had >95% power to detect any genetic correlation higher than .05 and 100% power to detect any genetic correlation higher than .10.

Next, we assessed the correlation between genetics of common epilepsy subtypes and cortical thickness and surface area in 34 cortical brain regions, regional brain volumes in 100 brain areas, five DTI measures in 21 white matter tracts, and four sulcal morphology parameters in various brain regions (Appendix S2). Only 121 of 2745 genetic correlations (4.4%) were nominally significant ( $p < .05$ ), which is less than expected purely by chance (i.e., 5%); none of these was significant when correcting for multiple testing (all  $p > .05/2745$ ).

## 4 | DISCUSSION

Here, we utilized the largest available GWASs to assess the genetic correlation between common epilepsy and structural brain measures. We did not find any genetic overlap between epilepsy and any measure of gray or white matter of the brain. These results suggest that the genetic basis of common epilepsy is distinct from the genetic basis of normal structural brain variation.

Previous studies that compared MRI scans between controls and people with focal and generalized epilepsy showed widespread, as well as regional and syndrome-specific, structural brain differences in white and gray matter of the brain.<sup>1,2</sup> It is known that the vulnerability for epilepsy, in particular generalized epilepsy, as well as the variance in gray and white matter MRI measures, is substantially explained by common genetic variants.<sup>3-5</sup>



**FIGURE 1** No genetic correlation was found between epilepsy and structural measures of brain volume, gray matter, or white matter of the whole brain. Genetic correlations were computed using linkage disequilibrium score regression, and the genetic correlation coefficients ( $\pm$ SE) are plotted on the x-axis. Rg, genetic correlation coefficient.

The absence of genetic overlap between epilepsy and MRI measures suggests that the genetic variation underlying structural brain differences between people does not meaningfully influence risk of epilepsy. Conversely, the findings also suggest that common genetic variants underlying susceptibility to epilepsy do not affect gray or white matter structural variation. Importantly, the lack of formal correlation may suggest that measured structural brain differences found in people with epilepsy are unrelated to the underlying genetic cause of the disease, and represent a separate source of information about epilepsy at group and individual levels. If so, structural brain differences are more likely a consequence of epilepsy or its treatment than its cause. For example, progressive cortical thinning is observed in patients with epilepsy, which might be due to seizure activity among other reasons.<sup>12</sup> Although frequent seizures are associated with more pronounced atrophy,<sup>13</sup> such atrophy is also found in patients who have become seizure-free.<sup>12</sup> A recent study found that cortical thinning in epilepsy is mediated by microglial activation.<sup>14</sup> Furthermore, transient depletion of activated microglia did not affect seizures, but did prevent cortical thinning, suggesting that these processes are distinct and potentially modifiable. Alternatively, treatment of epilepsy by antiepileptic drugs could also affect gray and white matter volume. For example, valproic acid, but not other antiepileptic drugs, has been associated with smaller gray and white matter volumes.<sup>15</sup>

Our study should be considered in light of some limitations. In this study, we only assessed common genetic variants (defined as a minor allele frequency > 1%) in common types of epilepsy. We cannot rule out the possibility that rare genetic variants or copy number variants contribute to both epilepsy risk and variation in brain measures, including during development. It is well known that some rare variants causing developmental epileptic encephalopathies (DEE), and other epilepsies, are associated with gross structural brain abnormalities, and some genes implicated in DEE have roles during brain development.<sup>16</sup> Similarly, focal epileptogenic lesions can be caused by rare genetic variants.<sup>17</sup> Because we only assessed genetics, we cannot rule out the influence of environmental or epigenetic factors that influence both epilepsy and brain structure. We used LDSC considering that it is the most established method to compute genetic correlations based on GWAS summary statistics. Novel alternatives such as High-Definition Likelihood (HDL) and GeNetic cOVariance Analyzer (GNOVA) produce almost identical genetic correlation estimates.<sup>18,19</sup> However, SEs can differ between these methods, and LDSC potentially has slightly lower statistical power to

detect significant associations. Due to data availability, we were not able to use genetic correlation methods based on individual-level data, which generally outperform summary statistics-based methods. Although we used the currently largest available GWASs of epilepsy and MRI measures, their sample sizes are still relatively modest compared to GWASs of more readily available phenotypes such as body mass index or height. Our study is large enough to exclude a large genetic correlation. However, we cannot exclude the possibility of a small genetic overlap between epilepsy and structural brain measures were a larger GWAS to be tested. Our analyses are based on epilepsy GWASs split into three broad categories. We did not have access to sufficiently powered GWASs of more resolved epilepsy subtypes; therefore, we are unable to rule out that there are genetic correlations between specific epilepsy subtypes (like mesial temporal lobe epilepsy) and structural brain measures. The focal epilepsy GWAS did not yield any genome-wide significant loci and demonstrated a low SNP-based heritability, which could have limited our statistical power to detect significant genetic correlations. The brain MRI GWASs that we used for our analyses were primarily based on population-based cohorts including <1% people with epilepsy. Therefore, we cannot exclude the possibility that there are epilepsy-specific genetic variants that influence both structural MRI measures and epilepsy risk.

Altogether, our results suggest that common epilepsies and structural brain variation have a distinct genetic basis. These results could aid in understanding the pathophysiology of epilepsy and associated structural brain changes. If structural brain changes in common epilepsy are the consequence of epilepsy rather than the cause, it would suggest that it is modifiable or even preventable. Potentially, preventing structural brain changes in epilepsy could reduce risk of comorbid psychiatric disorders or cognitive decline.

#### AUTHOR CONTRIBUTIONS

All authors contributed to the conception and design of the study. Remi Stevelink performed the statistical analyses. Bobby P. C. Koeleman and Sanjay M. Sisodiya supervised the analyses. All authors contributed to writing of the manuscript.

#### ACKNOWLEDGMENTS

We would like to thank the Ming Fund for providing funding for Remi Stevelink. We are grateful to the people with epilepsy and volunteers who participated in this research. The ILAE facilitated the Consortium on Complex Epilepsies through the Commission on Genetics and by

financial support; however, the opinions expressed in the article do not necessarily represent the policy or position of the ILAE.


### CONFLICT OF INTEREST STATEMENT

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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### SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Stevelink R, Koeleman BPC, Sisodiya SM, International League Against Epilepsy Consortium on Complex Epilepsies. Distinct genetic basis of common epilepsies and structural magnetic resonance imaging measures. *Epilepsia*. 2023;64:e82–e86. <https://doi.org/10.1111/epi.17529>