

Associations between epilepsy-related polygenic risk and brain morphology in childhood

Alexander Ngo,^{1,2} Lang Liu,^{1,3} Sara Larivière,⁴ Valeria Kebets,^{1,2} Serena Fett,^{1,2} Clara F. Weber,^{1,5,6} Jessica Royer,^{1,2} Eric Yu,^{1,3} Raúl Rodríguez-Cruces,^{1,2} Zhiqiang Zhang,⁷ Leon Qi Rong Ooi,^{8,9,10} B. T. Thomas Yeo,^{8,9,10} Birgit Frauscher,^{11,12} Casey Paquola,¹³ Maria Eugenia Caligiuri,¹⁴ Antonio Gambardella,¹⁵ Luis Concha,¹⁶ Simon S. Keller,^{17,18} Fernando Cendes,¹⁹ Clarissa L. Yasuda,¹⁹ Leonardo Bonilha,²⁰ Ezequiel Gleichgerrcht,²¹ Niels K. Focke,²² Raviteja Kotikalapudi,²³ Terence J. O'Brien,^{24,25} Benjamin Sinclair,^{24,25} Lucy Vivash,^{24,25} Patricia M. Desmond,²⁵ Elaine Lui,²⁵ Anna Elisabetta Vaudano,^{26,27} Stefano Meletti,^{26,27} Reetta Kälviäinen,^{28,29} Hamid Soltanian-Zadeh,^{30,31} Gavin P. Winston,^{32,33,34} Vijay K. Tiwari,³⁵ Barbara A. K. Kreilkamp,²² Matteo Lenge,³⁶ Renzo Guerrini,^{36,37} Khalid Hamandi,^{38,39} Theodor Rüber,^{40,41,42,43} Tobias Bauer,^{40,41,42} Orrin Devinsky,⁴⁴ Pasquale Striano,⁴⁵ Erik Kaestner,⁴⁶ Sean N. Hatton,⁴⁷ Lorenzo Caciagli,^{32,48} Matthias Kirschner,^{49,50} John S. Duncan,^{32,33} Paul M. Thompson,⁵¹ ENIGMA Consortium Epilepsy Working Group, Carrie R. McDonald,^{46,52} Sanjay M. Sisodiya,^{32,33} Neda Bernasconi,^{1,2} Andrea Bernasconi,^{1,2} Ziv Gan-Or^{1,2,3} and Boris C. Bernhardt^{1,2}

Abstract

Extensive neuroimaging research in temporal lobe epilepsy with hippocampal sclerosis (TLE-HS) has identified brain atrophy as a disease phenotype. While it is also related to a complex genetic architecture, the transition from genetic risk factors to brain vulnerabilities remains unclear. Using a population-based approach, we examined the associations between epilepsy-related polygenic risk for HS (PRS-HS) and brain structure in healthy developing children, assessed their relation to brain network architecture, and evaluated its correspondence with case-control findings in TLE-HS diagnosed patients relative to healthy individuals

We used genome-wide genotyping and structural T1-weighted magnetic resonance imaging (MRI) of 3,826 neurotypical children from the Adolescent Brain Cognitive Development (ABCD) study. Surface-based linear models related PRS-HS to cortical thickness measures, and subsequently

contextualized findings with structural and functional network architecture based on epicentre mapping approaches. Imaging-genetic associations were then correlated to atrophy and disease epicentres in 785 patients with TLE-HS relative to 1,512 healthy controls aggregated across multiple sites.

Higher PRS-HS was associated with decreases in cortical thickness across temporo-parietal as well as fronto-central regions of neurotypical children. These imaging-genetic effects were anchored to the connectivity profiles of distinct functional and structural epicentres. Compared with disease-related alterations from a separate epilepsy cohort, regional and network correlates of PRS-HS strongly mirrored cortical atrophy and disease epicentres observed in patients with TLE-HS, and highly replicable across different studies. Findings were consistent when using statistical models controlling for spatial autocorrelations and robust to variations in analytic methods.

Capitalizing on recent imaging-genetic initiatives, our study provides novel insights into the genetic underpinnings of structural alterations in TLE-HS, revealing common morphological and network pathways between genetic vulnerability and disease mechanisms. These signatures offer a foundation for early risk stratification and personalized interventions targeting genetic profiles in epilepsy.

Author affiliations:

1 Montreal Neurological Institute and Hospital, McGill University, Montreal, QC, H3A 2B4, Canada

2 Department of Neurology and Neurosurgery, McGill University, Montreal, QC, H3A 1A1, Canada

3 Department of Human Genetics, McGill University, Montreal, QC, H3A 1Y2, Canada

4 Centre de Recherche du CHUS, Université de Sherbrooke, Sherbrooke, QC, J1H 5N4, Canada

5 Department of Psychiatry and Psychotherapy, University of Lübeck, Lübeck, 23538, Germany

6 Centre of Brain, Behavior and Metabolism, University of Lübeck, Lübeck, 23562, Germany

7 Department of Medical Imaging, Nanjing University School of Medicine, Nanjing, 211166, China

- 1 8 Centre for Sleep and Cognition, National University of Singapore, Singapore, 117549
2 Singapore
- 3 9 Centre for Translational Magnetic Resonance, National University of Singapore, Singapore,
4 117549, Singapore
- 5 10 Department of Electrical and Computer Engineering, National University of Singapore,
6 Singapore, 117583, Singapore
- 7 11 Department of Neurology, Duke University, Durham, NC, 27710, USA
- 8 12 Department of Biomedical Engineering, Duke University, Durham, NC, 27708, USA
- 9 13 Institute of Neuroscience and Medicine (INM-7), Forschungszentrum Jülich, Jülich, 52428,
10 Germany
- 11 14 Neuroscience Research Center, University Magna Græcia, Catanzaro, 88100, Italy
- 12 15 Institute of Neurology, University Magna Græcia, Catanzaro, 88100, Italy
- 13 16 Institute of Neurobiology, Universidad Nacional Autónoma de México, Querétaro, 76230,
14 México
- 15 17 Institute of Systems, Molecular and Integrative Biology, University of Liverpool, Liverpool,
16 L69 7BE, UK
- 17 18 Walton Centre NHS Foundation Trust, Liverpool, L9 7LJ, UK
- 18 19 Department of Neurology, University of Campinas–UNICAMP, Campinas, São Paulo,
19 13083887, Brazil
- 20 20 Department of Neurology, Emory University, Atlanta, GA, 30322, USA
- 21 21 Department of Neurology, Medical University of South Carolina, Charleston, SC, 29425,
22 USA
- 23 22 Department of Neurology, University of Medicine Göttingen, Göttingen, 37075, Germany
- 24 23 Department of Neurology and Epileptology, Hertie Institute for Clinical Brain Research,
25 University of Tübingen, Tübingen, 72076, Germany
- 26 24 Department of Neuroscience, Central Clinical School, Alfred Hospital, Monash University,
27 Melbourne, Melbourne, VIC, 3004, Australia

- 1 25 Departments of Medicine and Radiology, The Royal Melbourne Hospital, University of
2 Melbourne, Parkville, VIC, 3050, Australia
- 3 26 Neurology Unit, OCB Hospital, Azienda Ospedaliera-Universitaria, Modena, 41126, Italy
- 4 27 Department of Biomedical, Metabolic and Neural Science, University of Modena and Reggio
5 Emilia, Modena, 41125, Italy
- 6 28 Epilepsy Center, Neuro Center, Kuopio University Hospital, Member of the European
7 Reference Network for Rare and Complex Epilepsies EpiCARE, Kuopio, 70210, Finland
- 8 29 Faculty of Health Sciences, School of Medicine, Institute of Clinical Medicine, University of
9 Eastern Finland, Kuopio, 70210, Finland
- 10 30 Control and Intelligent Processing Center of Excellence (CIPCE), School of Electrical and
11 Computer Engineering, University of Tehran, Tehran, 1439957131, Iran
- 12 31 Departments of Research Administration and Radiology, Henry Ford Health System, Detroit,
13 48202, USA
- 14 32 Division of Neurology, Department of Medicine, Queen's University, Kingston, ON, K7L
15 2V7, Canada
- 16 33 Department of Clinical and Experimental Epilepsy, UCL Queen Square Institute of
17 Neurology, London, WC1N 3BG, UK
- 18 34 Chalfont Centre for Epilepsy, Bucks, SL9 0RJ, UK
- 19 35 Institute for Molecular Medicine, University of Southern Denmark, Odense, s5230 Denmark
- 20 36 Neuroscience and Human Genetics Department, Meyer Children's Hospital IRCCS, Florence,
21 50139, Italy
- 22 37 University of Florence, Florence, 50121, Italy
- 23 38 The Wales Epilepsy Unit, Department of Neurology, University Hospital of Wales, Cardiff,
24 CF14 4XW, UK
- 25 39 Cardiff University Brain Research Imaging Centre (CUBRIC), College of Biomedical
26 Sciences, Cardiff University, Cardiff, CF24 4HQ, UK
- 27 40 Department of Epileptology, University of Bonn Medical Center, Bonn, 53127, Germany

- 41 Department of Neuroradiology, University of Bonn Medical Center, Bonn, 53127, Germany
- 42 German Center for Neurodegenerative Diseases, Göttingen, 37075, Germany
- 43 Center for Medical Data Usability and Translation, University of Bonn, Bonn, 53113, Germany
- 44 Department of Neurology, NYU Grossman School of Medicine, New York, NY, 10017, USA
- 45 Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genova, Genova, 16147, Italy
- 46 Department of Radiation Medicine and Applied Sciences, University of California San Diego, La Jolla, CA, 92093, USA
- 47 Department of Neurosciences, Center for Multimodal Imaging and Genetics, University of California San Diego, La Jolla, CA, 92093, USA
- 48 Department of Neurology, Inselspital, Sleep-Wake-Epilepsy-Center, Bern University Hospital, University of Bern, Bern, 3010, Switzerland
- 49 Department of Psychiatry, Psychotherapy and Psychosomatics, Psychiatric Hospital University of Zurich, Zurich, 8008, Switzerland
- 50 Division of Adult Psychiatry, Department of Psychiatry, Geneva University Hospitals, Geneva, 1205, Switzerland
- 51 Imaging Genetics Center, Mark & Mary Stevens Institute for Neuroimaging and Informatics, Keck School of Medicine, University of Southern California, Los Angeles, CA, 90033, USA
- 52 Department of Psychiatry, Center for Multimodal Imaging and Genetics, University of California San Diego, La Jolla, CA, 92093, USA

Correspondence to: Boris C. Bernhardt, PhD

3801 University Street, Montreal, Quebec, Canada H3A 2B4

Email: boris.bernhardt@mcgill.ca

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Introduction

Epilepsy is characterized by an enduring predisposition to recurrent spontaneous seizures and affects over 50 million people worldwide.¹ One of the most common forms of epilepsy is temporal lobe epilepsy (TLE), a focal epilepsy associated pathologically with hippocampal sclerosis (HS) and pharmaco-resistance. Cumulative evidence has underscored the complexity of TLE-HS, revealing contributions from genetic and acquired factors in epileptogenesis. With seizure onsets typically in childhood and adolescence,² developmental transitions spanning youth represent a key window for epilepsy risk. Adequately capturing the condition's effects on brain organization, particularly in development, may advance our understanding of brain mechanisms giving rise to seizures and may have important implications for disease monitoring and early diagnosis.

In addition to its typical association with mesiotemporal pathology, neuroimaging evidence in patients with TLE-HS has identified widespread structural alterations. Magnetic resonance imaging (MRI) analysis of brain morphology has established robust structural compromise in the hippocampus, subcortical regions, as well as more widespread temporal and fronto-central cortical systems. These findings were initially shown in single centre studies,^{3–6} and more recently confirmed in large-scale multisite consortia, notably ENIGMA-Epilepsy.^{7,8} The latter initiative has mapped consistent patterns of multilobar atrophy in TLE-HS, and further contextualized findings with measures of brain network architecture, confirming temporo-limbic regions as epicentres of distributed structural pathology.⁹ Despite a likely influence of environmental factors and clinical events on brain structure in TLE,¹⁰ there has been growing evidence of important genetic influence,¹¹ suggesting a possible mechanism affecting this classical disease phenotype.

Epilepsy has a complex genetic architecture, with many contributory genetic factors.^{12–16} Variants underlying many different monogenic forms of epilepsy are rare, yet of large effect that can confer high risk or be causally responsible for the disease.^{17,18} Despite the clinical implications of these variants, common epilepsy syndromes, particularly TLE-HS, rarely carry such variants and

1 presumably have a complex, multigenic inheritance.¹⁹ Causation may therefore be attributable to
2 the synergy of multiple genetic variants interacting with each other, together with acquired
3 environmental factors. Recent genome-wide association studies (GWAS) have identified common
4 risk alleles.^{13–16} These individual genetic risk variants are usually of small effect and cannot
5 quantify risk or inform prognosis and treatment.²⁰ However, genome-wide profiling using
6 polygenic risk scores (PRS) may provide a window into the genetic liability of the disease. By
7 estimating the combined effect of individual single nucleotide polymorphisms (SNPs), it can
8 collectively capture the variance explained by these common alleles and provide an individualized
9 measure of genetic risk.^{21–23} While previous studies have revealed enriched genetic vulnerability
10 for epilepsy in patients,^{24–26} the consequences of epilepsy susceptibility on disease phenotypes,
11 such as brain morphology, have not been systematically charted. Investigating this micro-to-
12 macroscale mechanism may provide insight into the translation of genetic vulnerability to disease
13 etiology or consequences.

14 In this study, we aimed to uncover the cumulative effects of epilepsy-related genetic risk variants
15 on structural brain organization during development. We analyzed structural MRI and genotyping
16 data in a large population-based cohort of neurotypical children from the Adolescent Brain
17 Cognitive Development study (ABCD).²⁷ To investigate associations between genetic risk factors
18 for epilepsy-related HS and brain-wide morphology, we generated PRS-related models of cortical
19 thickness and subcortical volume. Network contextualization further identified connectome
20 epicentres of PRS-HS effects—network pathways that may govern the genetically affected
21 morphological patterning. To pinpoint common processes between genetic risk and disease
22 pathologies, we employed spatial correlations with autocorrelation preserving null models and
23 related structural effects of PRS-HS to disease-related atrophy and epicentres derived from large
24 multi-site MRI-based datasets of patients and controls (**Fig. 1**).^{28–30}

1 **Materials and methods**

2 **Participants**

3 **Adolescent Brain Cognitive Development (ABCD).**

4 The present study used the demographic, genetic, and neuroimaging data of 3,826 unrelated
 5 neurotypical children (mean $\pm$ standard deviation [SD] age = 10.0 ± 0.6 years; 2,052 males) from
 6 the multisite ABCD 2.0.1 release³¹ and selected based on the availability of high-quality T1-
 7 weighted MRI and genome-wide genotyping data, as well as European genetic ancestry (described
 8 in the subsequent sections). Briefly, participants were recruited based on probability sampling of
 9 schools near the study sites. Parents or guardians provided written consent, while the child
 10 provided written assent. All aspects of the ABCD study were approved by the Institutional Review
 11 Board at the University of California, San Diego, United States. Overall, the large size of this
 12 cohort allows for unprecedented exploration of genetic risk for TLE-HS and its potential effects
 13 on brain organization in an *a priori* neurotypical child population.

14 **Human Connectome Project (HCP)**

15 We also selected 50 unrelated healthy adults from the HCP dataset (imaging acquisition and
 16 processing are described in the **Supplementary Materials**).³² Such initiatives provide normative
 17 structural and functional connectivity information to employ network epicentre mapping of PRS-
 18 HS.

19 **Enhancing Neuro Imaging Genetics through Meta Analysis Epilepsy**

20 **Consortium (ENIGMA-Epilepsy)**

21 Imaging-genetic associations from neurotypical children were compared to MRI-based disease
 22 effects observed between 732 patients with TLE and radiological evidence of HS (mean $\pm$ SD age
 23 = 38.6 ± 10.6 years; 329 males; 391 left-sided focus) and 1,418 (mean $\pm$ SD age = 33.8 ± 10.5
 24 years; 643 males) healthy controls (HC). Details of case-control cohorts are described in the
 25 **Supplemental Materials** and elsewhere.²⁸

1 Independent TLE-HS case-control datasets

2 To assess the replication of the aforementioned analysis, imaging-genetic associations were also
 3 compared to structural alterations observed between 53 individuals with pharmaco-resistant TLE-
 4 HS and 93 age- ($t = 1.51$, $p = 0.13$) and sex-matched ($\chi^2 = 0.13$, $p = 0.72$) healthy controls (HC).
 5 Case-control participants were selected from (i) Montreal Neurological Institute and Hospital
 6 (MICs; $n_{\text{TLE-HS/HC}} = 23/36$)²⁹ and (ii) Jinling Hospital (NKG; $n_{\text{TLE-HS/HC}} = 37/57$).³⁰
 7 Sociodemographic, clinical and imaging details of the two sites are in the **Supplementary**
 8 **Materials**.

9 Genomic data acquisition and processing of ABCD

10 SNP genotyping

11 A total of 550,000 SNPs were genotyped from saliva samples using the Affymetrix Axiom
 12 Smokescreen Array platform.^{33,34} The data were prepared for imputation using
 13 “imputePrepSanger” pipeline (<https://hub.docker.com/r/eauforest/imputePrepSanger/>),
 14 implemented on CBRAIN³⁵ and the Human660W-Quad_v1_A-b37-strand chip as reference.

15 Genotyping quality control and imputation

16 Genotyping was quality controlled using PLINK 1.9.³⁶ Steps included: (i) assessment of
 17 heterozygosity using the PLINK `--indep-pairwise` command with parameters set to 200, 50, and
 18 0.15; (ii) removal of samples whose heterozygosity F coefficient was greater than 3 SD units from
 19 the mean; (iii) removal of samples and SNPs with low call rate at 0.01 and all SNPs with minor
 20 allele frequency (MAF) < 0.01 ; (iv) removal of individuals with mismatched sex and gender; (v)
 21 exclusion of non-European individuals by PCA with Hapmap; (vi) removal of samples with a first-
 22 or second-degree relative in the cohort ($\pi > 0.125$); (vii) application of a haplotype-based test for
 23 non-random missing genotype data to remove SNPs at $p < 1 \times 10^{-4}$ where they had non-random
 24 associations between unobserved genotypes and missingness; and (viii) application of a test for
 25 Hardy-Weinberg equilibrium (HWE) and removal of SNPs significant at $p < 1 \times 10^{-6}$. Imputation
 26 was performed using the Michigan Imputation Service with the Haplotype Reference Consortium
 27 (HRC) r1.1 2016 (hg19) as a reference panel.³⁷

Deriving polygenic risk scores

Individualized PRS were computed using the summary statistics from an epilepsy genome-wide association study for focal epilepsy with documented HS.¹⁵ While this may not necessarily equate to TLE-HS, we used this classification as a close proxy given the high prevalence and relative specificity of HS in TLE. SNPs with an INFO < 0.8 and an MAF < 0.01 were excluded, and duplicate SNPs were removed. PRSice-2 was used to calculate genetic risk scores.³⁸ Given that an optimal probability threshold (P_{SNP}) related to HS was not previously reported, we used multiple P_{SNP} that significantly predicted focal epilepsy: 0.001, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5.²⁶ All main analyses used PRS constructed at $P_{\text{SNP}} < 0.1$, with consistency of findings evaluated across remaining thresholds.

Imaging acquisition and processing of ABCD

Acquisition

All participants underwent 3T MRI scanning with prospective motion correction to reduce head motion and distortions, including a 3D T1-weighted (T1w) anatomical scan based on a magnetization-prepared rapid acquisition gradient echo sequence.³¹

Processing

T1w data were processed using FreeSurfer (version 5.3.0) to generate cortical surface and subcortical segmentations.^{39,40} Based on the Desikan-Killiany anatomical atlas,⁴¹ subject-specific maps of cortical thickness were sampled across 68 grey matter brain regions, and volume measures were obtained from 12 subcortical gray matter regions (bilateral amygdala, caudate, nucleus accumbens, pallidum, putamen, and thalamus) and bilateral hippocampi.

Multisite data harmonization

Morphological data were harmonized across sites using ComBat (<https://github.com/Jfortin1/ComBatHarmonization>), a post-acquisition statistical batch normalization of between-site effects, while preserving age, sex and genetic risk.⁴²

1 Statistical analyses

2 Structural correlates of PRS-HS

3 We implemented surface-based linear models in BrainStat (version 0.4.2;
4 <https://brainstat.readthedocs.io/>)⁴³ with age, sex, and the first 10 genetic principal components as
5 covariates, similar to previous imaging-genetics studies.^{44–46} These related PRS-HS to cortical
6 thickness and subcortical volume in neurotypical children from ABCD. Multiple comparisons
7 were then corrected using the false discovery rate (FDR) procedure.⁴⁷

8 To assess potential hemispheric asymmetry in the association between PRS-HS and cortical
9 morphology, we computed interhemispheric asymmetric indices for thickness across homologous
10 regions: $AI = (left - right) / |(left + right)/2|$, where AI is asymmetry index and left and
11 right are the cortical thickness of left and right areas. Correlations between asymmetry and PRS-
12 HS were assessed using similar linear models.

13 Network substrates of PRS-related structural changes

14 We identified morphological polygenic risk epicentres by spatially correlating each brain region's
15 healthy functional and structural connectivity profiles from the HCP dataset to the imaging-genetic
16 map (*i.e.*, the unthresholded t-statistic map from the above analysis). This approach was repeated
17 systematically across all cortical and subcortical regions with non-parametric spin permutation
18 null models to control for spatial autocorrelation (5,000 repetitions),⁴⁸ implemented in the
19 ENIGMA toolbox (version 2.0.3; <https://enigma-toolbox.readthedocs.io/>).⁴⁹ Higher spatial
20 similarity between a given node's connectivity profile and whole-brain patterns of PRS-HS
21 vulnerability supported that the node was an epicentre.

22 *Dissociating the effects of network architecture from potential confounds introduced in*
23 *normative connectomes, we also generated PRS-related epicentres using TLE-specific structural*
24 *and functional connectomes (image processing and connectivity computations are described in*
25 *the **Supplementary Materials**).*

26 We identified the spatial overlap between imaging-genetic correlates from ABCD and epilepsy-
27 related alterations. The latter were obtained previously published statistical case-control atrophy
28 and epicentre maps for left and right TLE-HS from ENIGMA-Epilepsy.^{8,28} Spin permutation-

based testing (5,000 repetitions) assessed significant spatial associations between imaging-genetic and case-control effects, at the regional and network level.

We furthermore performed spatial correlations with case-control atrophy and epicentre maps for left and right TLE-HS from independent case-control datasets (MICs and NKG). Patient-specific morphology maps were *z*-scored relative to controls. We then used surface-based linear models with age, sex, and site as covariates to compare between groups. Subsequent epicentre analysis was performed on the TLE-HS atrophy profile. Spin permutation-based testing (5,000 repetitions) evaluated significant spatial correlations between imaging-genetic and case-control effects.^{48,49}

To evaluate the specificity of imaging-genetic effects to TLE-HS, we repeated the same analyses with idiopathic generalized epilepsy (IGE), another common epilepsy syndrome,²⁸ and six psychiatric disorders (attention deficit disorder [ADHD], autism spectrum disorder [ASD], bipolar disorder [BD], major depressive disorder [MDD], obsessive-compulsive disorder [OCD], and schizophrenia [SCZ]), all acquired from the ENIGMA Consortium.^{49,50} Correlation coefficients were statistically compared to those observed in TLE-HS using Fisher *z*-transformation. Significance testing of these correlations and their differences was assessed using spin permutation tests with 5,000 repetitions.^{48,49}

Transcriptomic associations

To investigate the molecular pathways that may link cortical vulnerability to disease atrophy, regional imaging-genetic and case-control patterns were related with gene expression derived from the ENIGMA toolbox,⁴⁹ which aggregates preprocessed *post-mortem* bulk microarray data from the Allen Human Brain Atlas.⁵¹ For each available gene ($n_{\text{total}} = 12,668$), we computed the spatial correlation between regional expression and imaging phenotype of interest (*i.e.*, PRS-mediated thinning and left/right TLE-HS atrophy). Based on autocorrelation-preserving null models ($n = 5,000$),^{48,49} we identified significantly correlated genes for both maps, and subsequently their intersection. A gene ontology enrichment analysis (<https://webgestalt.org>) was utilized to uncover biological processes enriched in the list of shared genes.⁵²

Robustness analyses

To verify that results were not biased by choosing a particular threshold, we repeated the PRS analyses and associations with case-control atrophy across all predictive P_{SNP} thresholds (0.001,

0.05, 0.1, 0.2, 0.3, 0.4, 0.5).²⁶ Specifically, PRS-HS was constructed at each threshold and spatial correlations between all pairs of imaging-genetic brain maps were performed. Spin permutation-based testing (5,000 repetitions) evaluated significant spatial correlations between imaging-genetic and case-control effects.^{48,49}

Results

Structural correlates of PRS-HS

We observed a significant and negative association between global cortical thickness and genetic vulnerability (left hemisphere: Pearson's correlation coefficient [r] = -0.041, $p_{\text{FDR}} < 0.05$; right hemisphere: $r = -0.044$, $p_{\text{FDR}} < 0.05$; **Fig. 2A**). Adopting a regional approach, these effects colocalized to bilateral temporal pole and postcentral gyrus, left precuneus, inferior parietal and lateral occipital regions as well as right superior and middle temporal, precentral and paracentral gyri (range $r = -0.0501 - -0.0362$, $p_{\text{FDR}} < 0.05$; **Fig. 2B**).

After correcting for multiple comparisons, no significant relationships between PRS-HS and subcortical and hippocampal volume (all $p_{\text{FDR}} \geq 0.05$; **Supplementary Fig. 1**), as well as morphological-related asymmetry was observed (all $p_{\text{FDR}} \geq 0.05$; **Supplementary Fig. 2**).

Network substrates of PRS-related structural changes

Given the large-scale effects of PRS-HS on cortical thickness, contextualizing imaging-genetic correlations with connectome architecture may provide insight into how localized genetic susceptibility propagates through distributed brain networks and predicts structural vulnerabilities. We systematically correlated imaging-genetic patterns (see *Fig. 2*) to the functional and structural connections of each cortical and subcortical region (**Fig. 3A**).⁴⁸ This implicated bilateral temporal-limbic and parietal cortices, amygdalae, hippocampi, and thalami as the most significant functional and structural epicentres (all $p_{\text{spin}} < 0.05$; **Fig. 3B**).

Network profiles were also similar when using TLE-specific connectomes (functional: $r = 0.86$, $p_{\text{spin}} < 0.001$; structural: $r = 0.98$, $p_{\text{spin}} < 0.001$; **Supplementary Fig. 3**).

1 Relation to epilepsy-specific atrophy and network epicentres

2 To link genetic vulnerability to disease alterations, we examined the spatial resemblance between
3 imaging-genetic findings to atrophy patterns observed in individuals with TLE-HS. Assessing
4 structural alterations in patients relative to controls (ENIGMA-Epilepsy), profound atrophy was
5 observed, with strongest effects in bilateral precuneus, precentral, paracentral, and temporal
6 cortices ($p_{FDR} < 0.05$; **Fig. 4A**). Correlating alteration maps with PRS effects (from ABCD, see
7 *Fig. 1*) showed significant overlap with left ($r = 0.63$, $p_{spin} = 0.001$) and right TLE-HS ($r = 0.59$,
8 $p_{spin} = 0.0006$; **Fig. 4B**).

9 Network mapping of atrophy (ENIGMA-Epilepsy) revealed significant temporo-limbic and
10 parieto-occipital epicentres in TLE-HS ($p_{FDR} < 0.05$; **Fig. 5A**). Similarly, imaging-genetic
11 epicentres (from ABCD, see *Fig. 2*) were strongly correlated with disease epicentres in left TLE-
12 HS (functional: $r = 0.95$, $p_{spin} < 0.001$; structural: $r = 0.78$, $p_{spin} < 0.001$), right TLE-HS (functional:
13 $r = 0.93$, $p_{spin} < 0.001$; structural: $r = 0.94$, $p_{spin} < 0.001$; **Fig. 5B**), suggesting potential pathway
14 convergence between PRS-HS and TLE-HS effects.

15 These region- and network-level correlations were highly consistent when correlating PRS effects
16 (from ABCD, see *Fig. 1* and *Fig. 2*) with separate, independent patient-control sites (MICs, NKG).
17 Comparison between PRS effects (from ABCD, see *Fig. 1*) and disease-related atrophy (**Fig. 4A**)
18 revealed moderate and highly significant positive correlations for left ($r = 0.50$, $p_{spin} = 0.0002$) and
19 right TLE-HS ($r = 0.41$, $p_{spin} = 0.009$; **Fig. 4B**). Imaging-genetic epicentres (from ABCD, see *Fig.*
20 *2*) were also strongly similar with disease epicentres (**Fig. 5A**) in left (functional: $r = 0.93$, $p_{FDR} <$
21 0.001 ; structural: $r = 0.77$, $p_{FDR} < 0.001$) and right TLE-HS (functional: $r = 0.89$, $p_{FDR} < 0.001$;
22 structural: $r = 0.89$, $p_{FDR} < 0.001$; **Fig. 5B**).

23 Cross-referencing our imaging-genetic patterns (From ABCD, see *Fig. 1* and *2*) with atrophy and
24 disease epicentre maps from IGE and six common psychiatric disorders, specificity analyses
25 showed that spatial correlations between PRS-HS and TLE-HS effects (see *Fig. 3* and *4*) were
26 statistically among the highest even when compared against the different conditions (**Table 1**;
27 IGE: **Supplementary Fig. 4**; psychiatric conditions: **Supplementary Fig. 5** and **6**).

Transcriptomic associations

Structural effects of PRS-HS shared a large number of genes with atrophy distributions in left ($n_{\text{overlapping}} = 2,274$, $p_{\text{FDR}} < 0.001$) and right ($n_{\text{overlapping}} = 2,264$, $p_{\text{FDR}} < 0.001$) TLE-HS. Ontological enrichment of these genes revealed biological processes involved in ion transmembrane transport, synaptic signaling, and neuronal development (all $p_{\text{FDR}} < 0.05$; **Supplementary Fig. 7**).

Robustness analyses

Our findings were not affected by varying the P_{SNP} thresholds ($n = 7$; 0.001, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5) used to construct individualized PRS-HS. Across the range of predictive thresholds, widespread decreases in thickness were related to PRS-HS, with strongest associations again in parietal and temporal regions (**Supplementary Fig. 8A**). Recapitulating the reliability of threshold-specific effects, we demonstrated high similarities among different thresholds (100.0% of correlations were significant, $p_{\text{spin}} < 0.05$). Moreover, we found comparable associations between imaging-genetic and cortical atrophy maps in left (89.2% of correlations were significant, $p_{\text{spin}} < 0.05$) and right TLE-HS (67.9% of correlations were significant, $p_{\text{spin}} < 0.05$; **Supplementary Fig. 8B**).

Translating this approach to network models of PRS-HS, temporo-limbic and parietal epicentres identified in the main analyses were consistent across different P_{SNP} thresholds (**Supplementary Fig. 9A**). The spatial distribution of these network epicentres was highly correlated with one another (100% of correlations were significant, $p_{\text{spin}} < 0.05$; **Supplementary Fig. 9B**).

Discussion

Emerging literature emphasizes the importance of genotype-phenotype associations in understanding the etiological mechanisms of epilepsy. Capitalizing on recent imaging-genetic initiatives, we combined genetic risk and whole-brain anatomy to characterize the polygenic burden of epilepsy-related HS in typical development. We found widespread decreases in cortical thickness associated with elevated PRS-HS, with the greatest effects in temporal and parietal regions. These imaging-genetic correlations were anchored to the connectivity profiles of fronto-parietal and temporo-limbic epicentres, and may play a crucial role in the network vulnerability of the brain. Structural correlates of PRS-HS further mirrored case-control atrophy and network

1 epicentres observed in patients with TLE-HS. Findings were replicable across different P_{SNP}
2 thresholds as well as different epilepsy case-control studies. Taken together, PRS-associated
3 structural vulnerabilities may represent an early biomarker for TLE-HS pathogenesis, offering new
4 avenues for risk stratification and pre-emptive interventions based on their genetic profiles.

5 Structural brain organization in typical development includes a complex, and genetically
6 determined cascade of changes from childhood to adolescence and ultimately to adulthood. Cross-
7 sectional and longitudinal characterization of cortical gray matter tissue has demonstrated global
8 and regional thinning during this period.^{53–57} Despite being an important aspect of normal
9 maturation, deviations from typical development have been associated with vulnerability for
10 various neurological and psychiatric conditions,^{58–60} including TLE-HS.^{61–63} While the exact
11 pathogenesis of TLE-HS remains unknown, genetic studies have characterized the role of common
12 susceptibility variants in patient cases.^{13–16} These variants account for a moderate proportion of
13 disease phenotypic variance, and may have adverse effects on structural brain development.¹⁵ Core
14 to our analytical framework is the association of individualized genetic risk profiling and mapping
15 of structural brain phenotypes, pinpointing the morphological vulnerabilities influenced by
16 underlying predisposition to the disease. Particularly relevant for a complex disorder that is
17 affected by many small-effect variants, PRS provides a personalized and compact measure of
18 overall genetic liability.^{21–23} Linked imaging-derived phenotypes would help visualize the
19 structural, biological impacts of common variant accumulation.²⁸ Examining a neurotypical
20 population, we identified widespread cortical thinning in children with elevated PRS-HS, and
21 conversely no relationship in the hippocampus: genetic risk may not be determinant or causative
22 of HS, but rather serve to influence the cortical alterations. These changes may reflect a
23 predisposition to developing a network of regions with greater propensity for epilepsy. Enrichment
24 of risk variants related to focal epilepsy have been reported in patients with early onset seizures.^{24,25}
25 Childhood-onset epilepsy has also been associated with widespread structural alterations
26 extending beyond the seizure focus.^{63,64} Given that thickness changes in development reflect
27 pruning and neuronal maturation,^{65–67} high genetic risk to TLE-HS may accelerate and alter
28 synaptic elimination and/or strengthening, potentially promoting an epileptogenic network.⁶⁸
29 Atypical structural modelling of the developing brain related to genetic risk may therefore help
30 predict a child's susceptibility to epilepsy.

While imaging-genetic analyses indicate significant associations between PRS-HS and structural brain changes, the observed effect sizes are relatively low, in line with those reported in previous studies across different, genetically mediated conditions.^{44–46,69} It is essential to consider the context of a typically developing cohort where the genetic burden of TLE-HS is reduced. The adverse impacts of risk variants on brain structure may be more subtle than those observed in a patient population with cumulative consequences of genetic, environmental, and disease-related factors. Moreover, it is difficult to identify the predictive value of PRS-related morphological changes in disease onset without systematic long-term clinical follow up. Ideally, the latter would have sufficient depth to determine a potential future epilepsy conversion of individuals initially deemed as neurotypical. Longitudinal patient-level data containing both genetics and imaging, prior and subsequent to disease onset, are necessary to address the pivot from PRS-related changes to clinically relevant phenotypes, but have not been collected to date at large scale. Despite these methodological challenges, using a population-based cohort, such as ABCD, provides a starting point to detect these relationships and improve our understanding of how genetic predispositions associated with certain clinical phenotypes correlate with brain structural vulnerabilities at the population level.

Alterations in TLE-HS commonly implicate many brain regions organized within interconnected systems.^{7,9,70–75} Understanding these interactions and their contributions to epileptogenesis requires the integration of connectome architecture. Epicentre mapping emerges as a valuable data-driven method to pinpoint critical regions—termed epicentres—that may serve as critical anchors in the manifestation of common genetic variants.^{9,76–78} Analyzing how localized genetic vulnerabilities propagate through distributed brain regions can identify potential network pathways that link genetic risk to pathological mechanisms. In particular, marked PRS-related thinning occurs in regions strongly connected to temporo-limbic and parietal territories. Diffusion MRI is highly effective at detecting long-range fibre bundles and direct monosynaptic structural connections, but it does not fully capture short-range intracortical and spatially distributed polysynaptic cortical systems.⁷⁹ By contrast, resting-state functional MRI can detect functional connectivity in the absence of direct structural connections, and thus is more informative about polysynaptic configurations.^{80,81} These temporo-limbic and parietal epicentres are characterized by a disproportionately high number of mono- and polysynaptic connections and serve as crucial areas for the integration and signal broadcasting across different structural and functional

1 networks. Consequently, such regions are inherently vulnerable to TLE-HS pathology.^{9,74,82} Given
 2 the convergence between functional and structural genetic epicentres, these regions also show
 3 susceptibility to the effects of accumulated genetic risk factors. Local changes related to PRS-HS
 4 may therefore disrupt global network organization, such that it increases vulnerability to targeted
 5 hub attacks, and potentially to seizure activity. The spatial and system-level context provided by
 6 these imaging-genetic associations—beyond PRS alone—may help identify vulnerable circuits for
 7 enhanced monitoring and neuromodulatory therapeutics.⁸³

8 To bridge the transition from genetic vulnerability to clinical phenotype, we contextualized
 9 regional and network correlates of PRS with case-control atrophy and epicentres, revealing strong
 10 spatial resemblance: thinner areas in children with elevated genetic risk tend to be thinner in
 11 patients and be highly connected to disease-related networks. Structural alterations have been
 12 consistently identified in TLE-HS, and are most marked in mesiotemporal, limbic, and
 13 sensorimotor areas.^{3–7,83} These alterations are also anchored to the connectivity profiles of distinct
 14 temporo-limbic and parietal epicentres.⁹ While family-based studies have shown low heritability
 15 for these atrophy patterns in healthy relatives,^{84–86} these predisposed regions may be too subtle and
 16 difficult to capture in endophenotype paradigms due to the complexity of epilepsy. Large sample
 17 sizes with varying genetic risk, as utilized herein, are required to characterize these imaging-
 18 genetic associations.⁸⁷ In combination with disease contextualization, we found a common driving
 19 process between genetic risk manifestations and disease effects. The polygenic burden of TLE-HS
 20 may therefore impact biological mechanisms—neuronal signaling, ion transport, and
 21 neurodevelopmental pathways as identified in transcriptomic associations—underlying brain
 22 structure and network architecture, and potentially influence disease vulnerability and
 23 pathogenesis. Although insufficient to cause TLE-HS alone due to its multifaceted components,
 24 genetics may increase susceptibility to the consequences of external factors^{20,88} in vulnerable
 25 regions and their networks through specific biological pathways.

26 Imaging-genetic associations also mirrored IGE-related atrophy and epicentres, to a lesser extent
 27 than TLE-HS. Pleiotropy—whereby a genetic variant influences multiple traits—occurs in the
 28 genetics of complex traits and disorders.^{89,90} Relevant to epilepsy, certain genetic variants may
 29 contribute to the vulnerability to both generalized and focal syndromes.¹⁵ Despite the wide clinical
 30 spectrum of epilepsy, the shared genetic architecture may play a role in some common pathological
 31 features.⁹¹ Supported by literature demonstrating similar patterns of cortical thinning across

different subtypes,⁷ our imaging-genetic model further adds to a common structural signature, such that widespread atrophy may originate from shared genetic pathways and reflect a more general epilepsy-related phenomenon. Similarly shown with disease epicentres herein, such a concept may also translate to network-level alterations. These associations may be potential biomarkers and encourage further exploration of the shared and trait-specific effects of common genetic factors in TLE-HS and the broader spectrum of epilepsy.

Specificity of these associations was supported by the fact that spatial correlations between imaging-genetic effects and disease effects in TLE-HS ranked the highest compared to several common psychiatric disorders. Many neurological and psychiatric conditions exhibit converging spatial patterns of cortical changes and network profiles, commonly colocalizing to higher-order, transmodal regions which are known to serve as epicentres of network organization and vulnerability.^{92,93} Regional pathological processes might propagate from common disease epicenters to connected brain regions leading to network-spreading patterns of cortical alterations.^{9,76–78,94–96} These centrally located areas in the network are therefore particularly vulnerable to pathophysiological perturbations and may explain the statistical significance of multiple correlations in our analyses. However, the consistent and greater associations of PRS-HS with TLE-HS suggest that—despite the broad involvement of distributed brain networks—there may be a disease-specific signature in the imaging-genetic associations that reflects meaningful biological specificity.

Limitations of imaging-genetic associations with respect to the GWAS-identified SNPs need to be highlighted. Firstly, summary statistics used for PRS calculation was based on GWAS of “focal epilepsy with documented HS”.¹⁵ Although it represents the most common pathological substrate for TLE-HS, hippocampal alterations occur in other epilepsy syndromes, and may be a cause, or consequence of epilepsy, or both.^{10,97,98} This phenotypic heterogeneity may impact the genetic associations identified. A more accurate delineation is crucial for detecting variants related to TLE-HS and its downstream effects, which may not be fully captured in our PRS correlations. Secondly, the same GWAS was mainly conducted in individuals of European ancestry.¹⁵ While our findings may be specific to European populations, they may not generalize to other under-represented groups.⁹⁹ Replication of imaging-genetic effects, particularly using a GWAS that includes larger and more diverse cohorts—ideally with inclusion criteria that specifically define TLE-HS—could enhance the reliability and generalizability of imaging-genetic effects. This would improve the

power to detect smaller effect sizes and refine the understanding of how specific genetic variants influence brain structure.

In summary, the present work highlights the potential for applying imaging-genetic frameworks to uncover interplay between genetic predisposition, neuroanatomical changes, and epilepsy pathogenesis. Structural vulnerabilities linked to high PRS-HS in childhood resembled atrophy and epicentres commonly observed in patients. Collectively, these results highlight important candidates for stratification efforts that can unravel the complex etiology of epilepsy, advancing the use of PRS as a potential biomarker for disease risk and for developing targeted interventions that prevent or limit progression of epilepsy.

Data availability

Genotyping and imaging data is available from the ABCD study upon application through NIMH Data Archive (<https://nda.nih.gov/>). GWAS summary statistics are available at http://www.epigad.org/gwas_ilae2018_16loci.html. The HCP dataset is available at <https://db.humanconnectome.org/>. Neuroimaging data from the ENIGMA (meta-analysis of summary statistics) are available for download (<https://github.com/MICA-MNI/ENIGMA>).

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Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

Appendix 1

Additional members of ENIGMA Consortium Epilepsy Working Group: Eugenio Abela, Julie Absil, Saud Alhusaini, Sarah J. A. Carr, Gianpiero L. Cavalleri, Esmaeil Davoodi-Bojd, Norman Delanty, Chantal Depondt, Colin P. Doherty, Martin Domin, Sonya Foley, Aoife Griffin, Graeme D. Jackson, Magdalena Kowalczyk, Angelo Labate, Soenke Langner, Mario Mascalchi, Pascal Martin, Mark P. Richardson, Christian Rummel, Mira Semmelroch, Mariasavina Severino, Aditi Singh, Rhys H. Thomas, Manuela Tondelli, Domenico Tortora, Felix von Podewills, Sjoerd B. Vos, Christopher D. Whelan, Roland Wiest, Junsong Zhang.

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Figure legends

Figure 1 Overview of study design. Regional and epicentre profiles of imaging-genetic associations (*left*) are correlated to disease effects observed in case-control studies (*right*). HC, healthy control; SNP, single nucleotide polymorphism; TLE-HS, temporal lobe epilepsy with hippocampal sclerosis.

Figure 2 PRS-HS associations with cortical thickness (ABCD). (A) Distribution of genetic risk effects on morphology across the different lobes (in order from top to bottom: all, frontal, limbic, occipital, parietal, temporal). (B) Regional imaging-genetic correlations between PRS-HS and thickness. Blue and red colours represent negative and positive correlations, respectively. White outline indicates $p_{FDR} < 0.05$. L, left; PRS-HS; polygenic risk score for epilepsy-related hippocampal sclerosis; R, right.

Figure 3 Network epicentres of morphological changes associated with PRS-HS. (A) Schematic representation of epicentre mapping approach using seed-based cortico- and subcortico-cortical connectivity. PRS-HS, polygenic risk score for epilepsy-related hippocampal sclerosis.

(B) Correlation coefficients indexing spatial similarity between imaging-genetic effects and seed-based functional (*top*) and structural (*bottom*) connections for every cortical and subcortical region. Red and blue colours represent negative associations, while grey depicts positive correlations. White outline indicates $p_{\text{spin}} < 0.05$. L, left; R, right.

Figure 4 Comparison between PRS-HS effects and epilepsy case-control atrophy. (A) Case-control differences in left and right TLE-HS from ENIGMA-Epilepsy (*top*) and from MICs and NKG (*bottom*). Blue and red colours point to atrophy and hypertrophy in patients relative to healthy controls, respectively. Outline in white represents $p_{\text{FDR}} < 0.05$. L, left; R, right; TLE-HS, temporal lobe epilepsy with hippocampal sclerosis. (B) Spatial correlations between epilepsy-related atrophy (*top*: ENIGMA-Epilepsy; *bottom*: MICs and NKG) and imaging-genetic effect maps (ABCD) are compared against permutation-based null correlations. Points represent the empirical correlation (with significance defined as $p_{\text{spin}} < 0.05$). In the boxplots, the ends of boxes represent the first (25%) and third (75%) quartiles, the centre line (median) represents the second quartile of the null distribution ($n = 5,000$ permutations), the whiskers represent the non-outlier endpoints of the distribution.

Figure 5 Comparison between imaging-genetic and epilepsy-related disease epicentres. (A) Functional and structural disease epicentres in left and right TLE-HS from ENIGMA-Epilepsy (*top*) and from MICs and NKG (*bottom*). Red and blue colours represent negative associations, while grey depicts positive correlations. Outline in white represents $p_{\text{spin}} < 0.05$. L, left; R, right; TLE-HS, temporal lobe epilepsy with hippocampal sclerosis. (B) Spatial correlations between epilepsy-related (*top*: ENIGMA-Epilepsy; *bottom*: MICs and NKG) and imaging-genetic epicentre maps (ABCD) are compared against permutation-based null correlations. Points represent the empirical correlation (with significance defined as $p_{\text{spin}} < 0.05$). In the boxplots, the ends of boxes represent the first (25%) and third (75%) quartiles, the centre line (median) represents the second quartile of the null distribution ($n = 5,000$ permutations), the whiskers represent the non-outlier endpoints of the distribution.

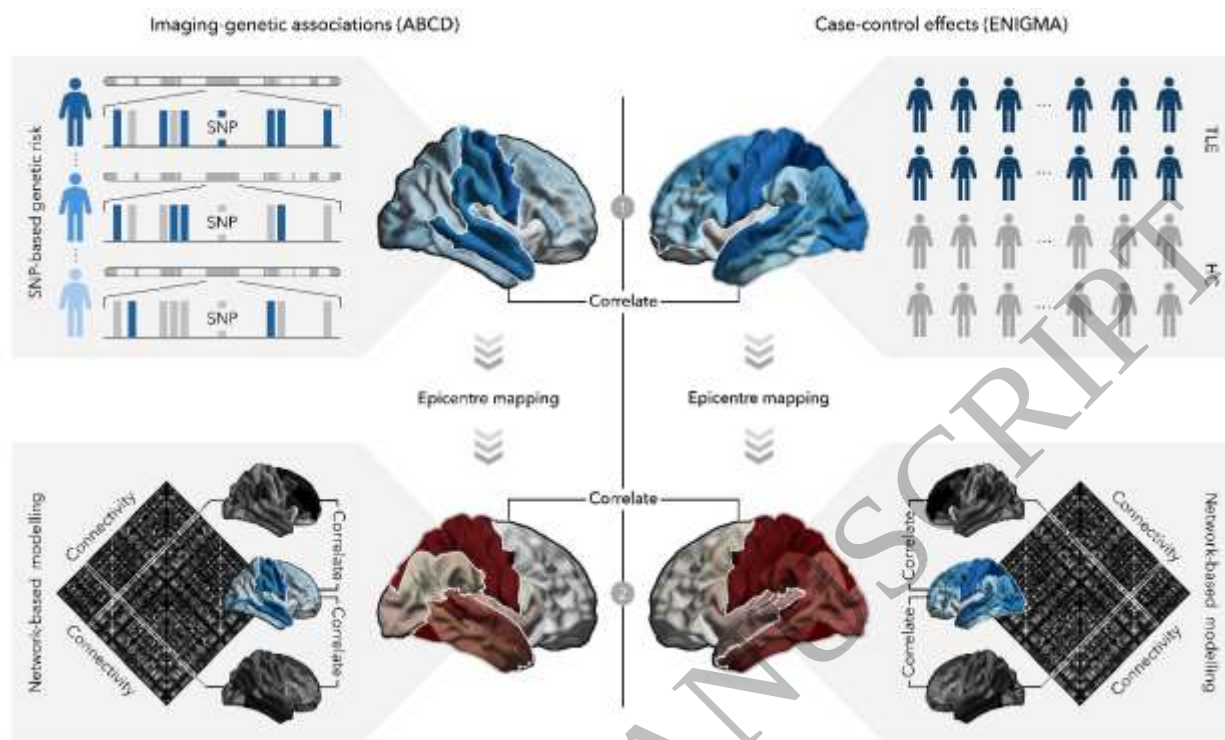
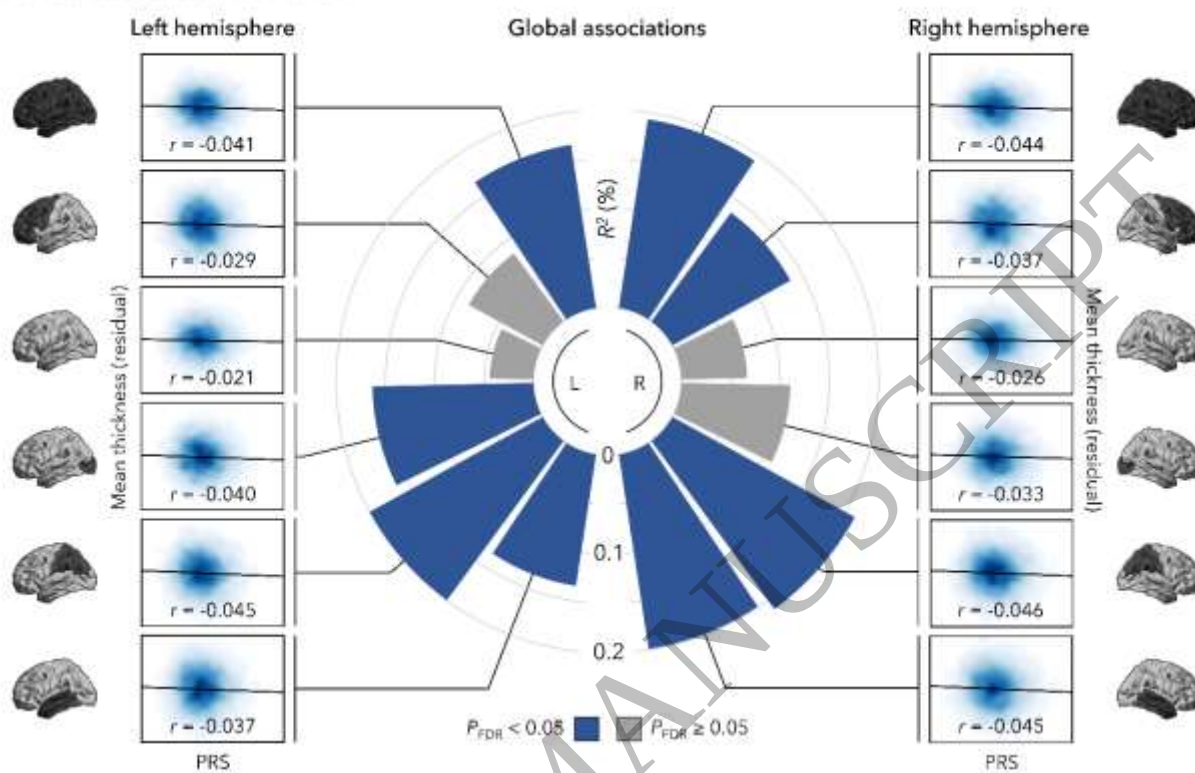


Figure 1
559x334 mm (x DPI)

A Brain-wide effects of PRS-TLE



B Local effects of PRS-TLE

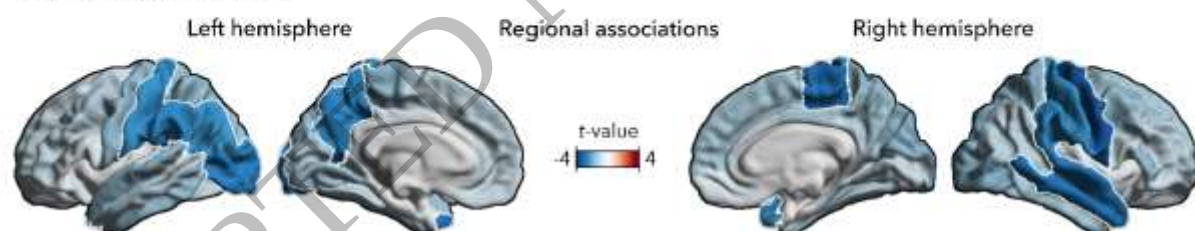
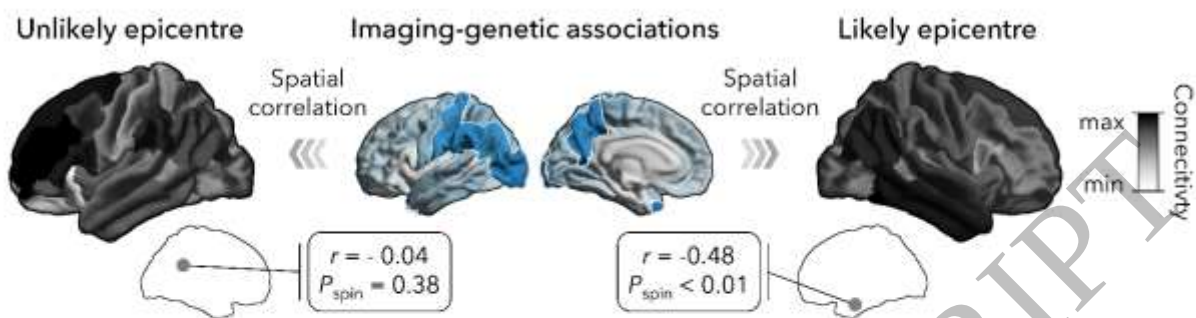


Figure 2
559x506 mm (x DPI)

A Network-based modelling of PRS-related structural shifts



B Functional and structural polygenic epicentres

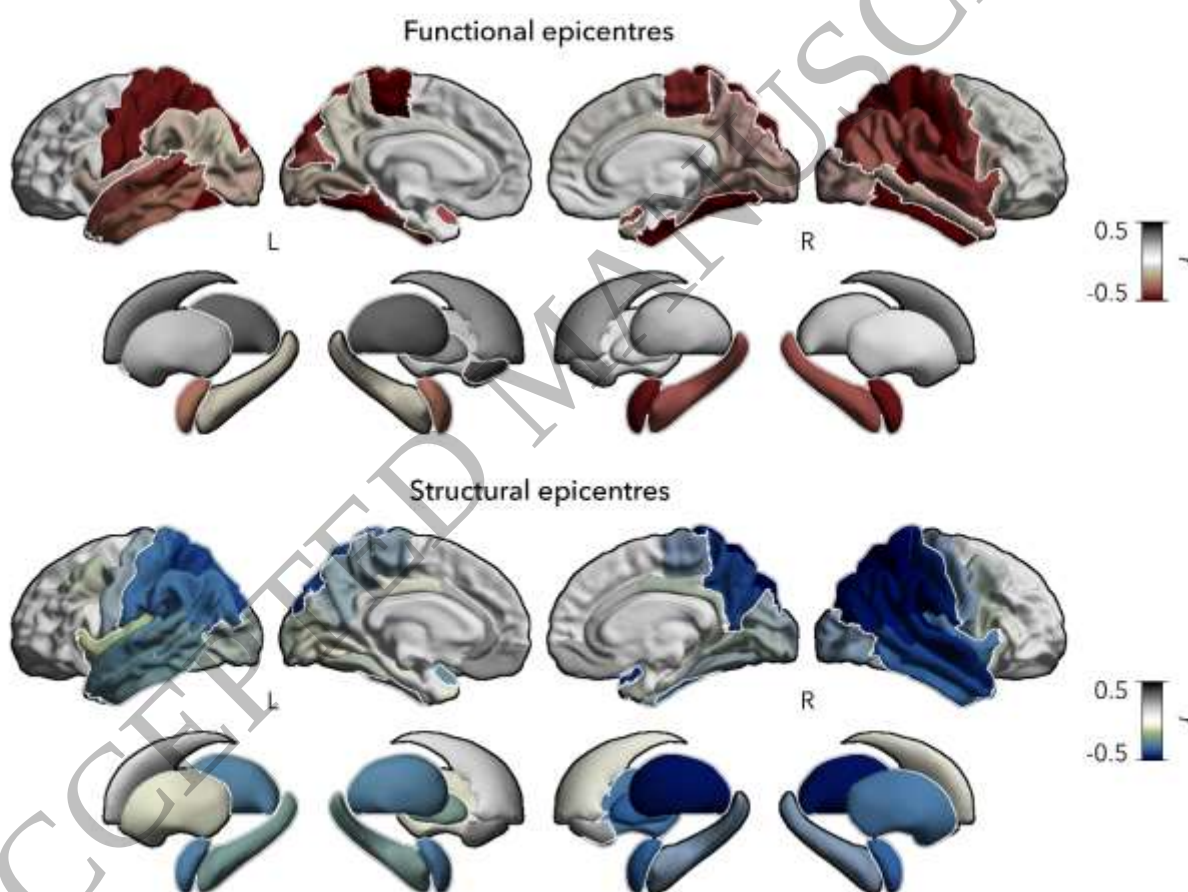


Figure 3
221x245 mm (x DPI)

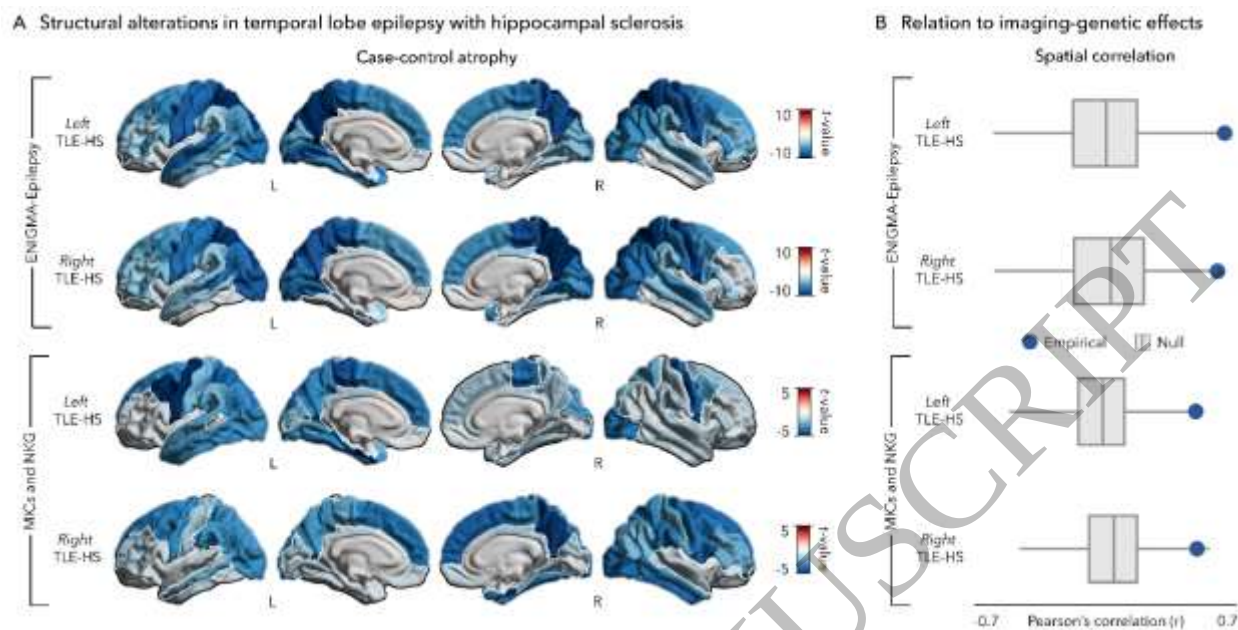


Figure 4
364x184 mm (x DPI)

1

Table 1 Spatial correlation between effects of PRS-HS and different conditions

Analysis	Correlation (r)	P-value (p_{spin})	Comparison to TLE-HS (p_{LR})
Idiopathic generalized epilepsy (IGE)			
Regional	0.42	0.004	0.306 / 0.449
Functional epicentre	0.76	<0.001	0.004 / 0.005
Structural epicentre	0.70	<0.001	0.39 / 0.002
Attention deficit/hyperactivity disorder (ADHD)			
Regional	-0.29	0.071	<0.001 / <0.001
Functional epicentre	-0.80	<0.001	<0.001 / <0.001
Structural epicentre	-0.67	<0.001	<0.001 / <0.001
Autism spectrum disorder (ASD)			
Regional	0.14	0.322	0.0751 / 0.133
Functional epicentre	0.84	<0.001	0.015 / 0.06
Structural epicentre	0.71	<0.001	0.36 / 0.002
Bipolar disorder (BD)			
Regional	0.08	0.328	0.014 / 0.039
Functional epicentre	-0.15	0.076	<0.001 / <0.001
Structural epicentre	-0.33	0.011	<0.001 / <0.001
Major depressive disorder (MDD)			
Regional	-0.41	0.005	<0.001 / <0.001
Functional epicentre	-0.72	<0.001	<0.001 / <0.001
Structural epicentre	-0.86	<0.001	<0.001 / <0.001
Obsessive compulsive disorder (OCD)			
Regional	-0.13	0.171	<0.001 / <0.001
Functional epicentre	-0.38	<0.001	<0.001 / <0.001
Structural epicentre	-0.69	<0.001	<0.001 / <0.001
Schizophrenia (SCZ)			
Regional	0.17	0.184	0.044 / 0.092
Functional epicentre	0.41	0.002	0.001 / <0.001
Structural epicentre	0.60	<0.001	0.218 / <0.001

2

Efficacy made Convenient



TYSABRI SC injection with the potential to administer **AT HOME** for eligible patients*

Efficacy and safety profile comparable between TYSABRI IV and SC^{†,2}

[†]Comparable PK, PD, efficacy, and safety profile of SC to IV except for injection site pain.^{1,2}

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A Biogen developed and funded JCV antibody index PML risk stratification service, validated and available exclusively for patients on or considering TYSABRI.



*As of April 2024, TYSABRI SC can be administered outside a clinical setting (e.g. at home) by a HCP for patients who have tolerated at least 6 doses of TYSABRI well in a clinical setting. Please refer to section 4.2 of the SmPC.¹

TYSABRI is indicated as single DMT in adults with highly active RRMS for the following patient groups:^{1,2}

- Patients with highly active disease despite a full and adequate course of treatment with at least one DMT
- Patients with rapidly evolving severe RRMS defined by 2 or more disabling relapses in one year, and with 1 or more Gd+ lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI

Very common AEs include nasopharyngitis and urinary tract infection. Please refer to the SmPC for further safety information, including the risk of the uncommon but serious AE, PML.^{1,2}

Abbreviations: **AE:** Adverse Event; **DMT:** Disease-Modifying Therapy; **Gd+:** Gadolinium-Enhancing; **HCP:** Healthcare Professional; **IV:** Intravenous; **JCV:** John Cunningham Virus; **MRI:** Magnetic Resonance Imaging; **PD:** Pharmacodynamic; **PK:** Pharmacokinetic; **PML:** Progressive Multifocal Leukoencephalopathy; **RRMS:** Relapsing-Remitting Multiple Sclerosis; **SC:** Subcutaneous.

References: 1. TYSABRI SC (natalizumab) Summary of Product Characteristics. 2. TYSABRI IV (natalizumab) Summary of Product Characteristics.

Adverse events should be reported. For Ireland, reporting forms and information can be found at www.hpra.ie. For the UK, reporting forms and information can be found at <https://yellowcard.mhra.gov.uk/> or via the Yellow Card app available from the Apple App Store or Google Play Store. Adverse events should also be reported to Biogen Idec on MedInfoUKI@biogen.com 1800 812 719 in Ireland and 0800 008 7401 in the UK.