

Supplementary Methods

Image preprocessing

All images underwent visual inspection to exclude those with visible artifacts, excessive head motion, segmentation inaccuracies, structural-functional registration discrepancies, or incomplete brain coverage. Before performing the preprocessing workflow, the 7T data underwent bias field correction using in-house software, originally developed by Lankinen K et al.¹, and implemented in Matlab 2019b (The MathWorks, Inc., Natick, Massachusetts, USA). The preprocessing of fMRI data was first conducted using the fMRIPrep 24.0.1 workflow², which was based on Nipype 1.8.6³. The fMRIPrep pipeline uses a combination of tools from well-known software packages, including FSL⁴, ANTs⁵, FreeSurfer⁶ and AFNI⁷. The input dataset was converted into valid BIDS format as required. The preprocessing pipeline included the following steps: (i) anatomical data preprocessing: a single T1-weighted (T1w) image was corrected for intensity non-uniformity using N4BiasFieldCorrection⁸ and skull-stripped using antsRegistration (ANTs 2.5.1); brain tissue was segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) using FAST (FSL 6.0.6), and brain surfaces were reconstructed with recon-all (FreeSurfer 7.3.2). ANTs-derived brain masks and FreeSurfer-derived GM segmentations were reconciled using a custom variation of the Mindboggle method⁹. Nonlinear registration with ANTs was used for volume-based spatial normalization to standard spaces (MNI152NLin6Asym and MNI152NLin2009cAsym). (ii) Functional data preprocessing: Includes the following steps: (a) Head-motion estimation: A reference BOLD volume was generated using a custom methodology of fMRIPrep for motion correction. Head-motion parameters (transformation matrices and six rotation/translation parameters) were estimated with mcflirt (FSL)¹⁰. (b) Slice time correction: Slice time correction was performed using 3dTShift (AFNI). All slices were realigned in time to the middle of each TR. (c) Normalization: First, the BOLD reference was co-registered to the T1-weighted reference using bbregister (FreeSurfer) with boundary-based registration¹¹. Then, functional datasets were normalized to the

MNI152NLin6Asym standard space using deformation fields estimated during anatomical preprocessing. Finally, functional time-series were resampled onto the fsLR template using Connectome Workbench and processed into grayordinate files¹², while volumetric data were resampled using cubic B-spline interpolation with nitransforms. (d) Confounds estimation: Confounding time-series, including framewise displacement (FD), DVARS and three region-wise global signals, were calculated. Framewise displacement (FD) and DVARS were calculated using Nipype¹³. Global signals from WM, CSF, and the whole brain, were extracted for nuisance regression. Physiological noise regressors were calculated with CompCor¹⁴, using high-pass filtered time-series, while probabilistic masks of CSF, WM, and GM were refined to exclude minimal GM volume, Motion outliers exceeding thresholds (FD > 0.5 mm, DVARS > 1.5,) were annotated. (e) The cifti outputs were generated at 91k surface density resolution.

Then the eXtensible Connectivity Pipeline- DCAN (XCP-D)^{15,16} was used to post-process the outputs of fMRIPrep. XCP-D was built with Nipype³. For each of the one BOLD runs found per subject, the following post-processing was performed:

(i) First, 36 nuisance regressors were selected based on the '36P' strategy, including six motion parameters, global signal, white matter signal, cerebrospinal fluid signal with their temporal derivatives, and quadratic expansions of motion parameters and tissue signals^{17,18}. (ii) The BOLD data were converted to NIfTI format, despiked using AFNI's 3dDespike, and then converted back to CIFTI format. (iii) Nuisance regressors were regressed out using a denoising method based on Nilearn's approach, followed by band-pass filtering with a second-order Butterworth filter (0.01-0.08 Hz) and linear regression for further denoising. (iv) The ALFF maps were smoothed using a Gaussian kernel with a full width at half maximum (FWHM) of 2 mm.

Cortical MRI measurements and statistical analysis

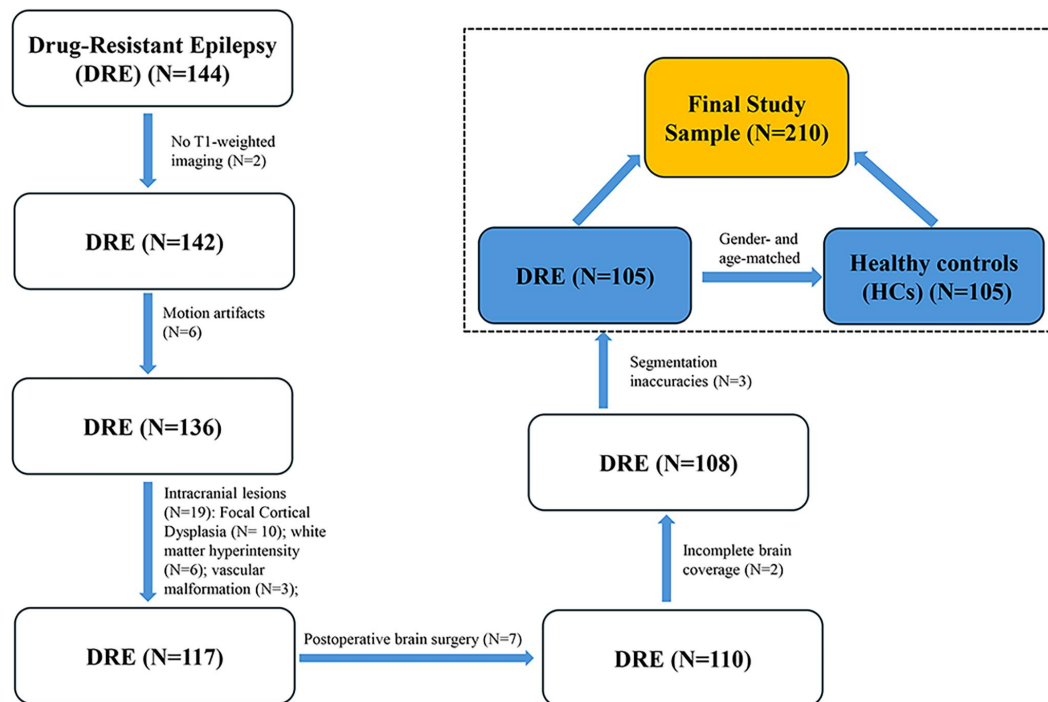
This study used 7T rs-fMRI data to calculate the vertex-wise mean ALFF (mALFF) and ReHo for each participant, followed by statistical comparison analysis. The ALFF¹⁹ was computed by transforming the denoised time series into the frequency

domain, calculating the power spectrum within the 0.01-0.08 Hz band, and obtaining vertex-wise ALFF values. To standardize, the value of each vertex in the ALFF maps was divided by the respective global mean value, yielding standardized ALFF maps (mALFF)²⁰. ReHo was defined as the Kendall's coefficient of concordance (KCC) of the time course of a given vertex with those of its nearest neighbors²¹, and was calculated using surface-based 2dReHo²² for cortical data and AFNI's 3dReHo²³ for subcortical regions. The 91k-resolution surface data were resampled to 64k to facilitate computational efficiency and ensure compatibility with common analysis frameworks. A fixed-effect model was applied within the Spatial Linear Modeling (SLM) framework to analyze group differences in cortical mALFF and ReHo between DRE and HCs. To control false positives, random field theory (RFT) correction²⁴ was applied, with a cluster-forming threshold of 0.001 and requiring a cluster size greater than 100 vertices to detect significant clusters. The SLM model was then fitted to the data to identify spatially significant group differences while accounting for spatial dependencies in the data, with site, gender, and age included as covariates.

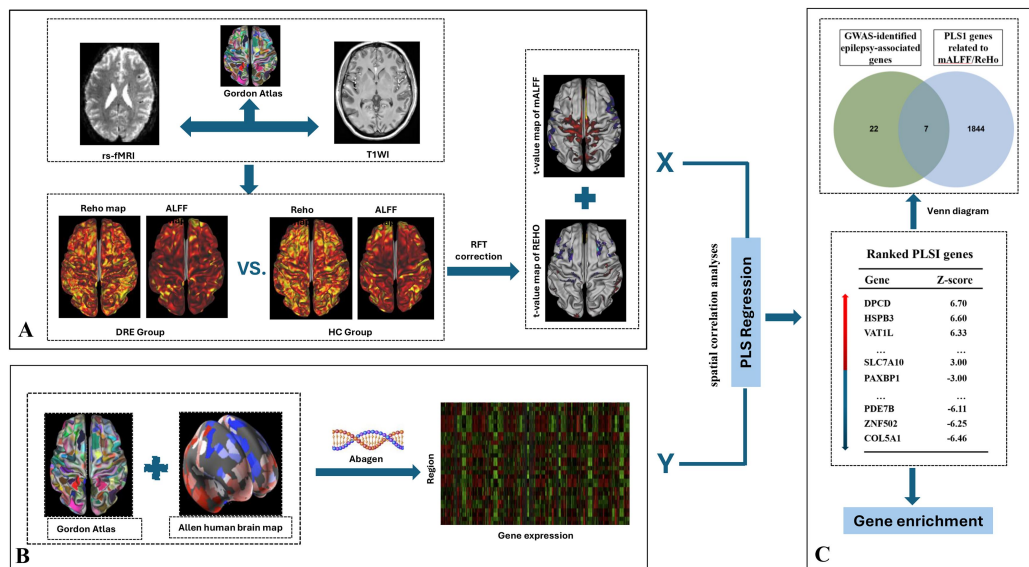
List of 29 Epilepsy-Associated Genes Identified in Recent GWAS

The 29 genes associated with epilepsy identified in the recent genome-wide association study (GWAS) were as follows:

BCL11A, SCN1A, RORB, KCNIP2, RYR2, CHRM3, POU3F3, GLS, STAC, CACNA2D2, PCDH7, KCNN2, SPOCK1, PTPRK, SUGCT, RMI1, SCN8A, RBFOX1, ARHGEF15, CDK5RAP3, AP3D1, TMPRSS15, GRIK1, FAM19A5, GABRA2, RSPO2, TMEM74, STX1B, CACNA1L.



Supplementary Figure 1 The data inclusion flowchart.



Supplementary Figure 2 This workflow aims to explore links between brain imaging, genes, and epilepsy. **(A)** Compares brain activity (ReHo/ALFF) in drug resistant epilepsy (DRE) vs. healthy control (HC) groups using fMRI. Maps are adjusted (RFT correction) to find PLS1 - related brain regions. **(B)** Integrates brain atlases (Gordon + Allen) to analyze regional gene expression (via Abagen). **(C)** Uses PLS regression to get PLS1 genes, which capture the strongest links between gene expression and neural

activity changes. Then, it overlaps epilepsy - linked genes (from GWAS) with these PLS1 genes, lists top PLS1 genes, and runs enrichment analysis to find functional themes.

Supplementary References

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