# Title page

**Title: White matter abnormalities across different epilepsy syndromes in adults: an ENIGMA Epilepsy study**

**Short Title: White matter across epilepsy syndromes**

**Authors**
Sean N Hatton[1], Khoa H Huynh[2], Leonardo Bonilha[3], Eugenio Abela[4], Saud Alhusaini[5,6], Andre Altmann[7], Marina KM Alvim[8], Akshara R Balachandra[9,10], Emanuele Bartolini[11,12], Benjamin Bender[13], Neda Bernasconi[14], Andrea Bernasconi[14], Boris Bernhardt[15], Núria Bargallo[16], Benoit Caldairou[14], Maria Eugenia Caligiuri[17], Sarah JA Carr[18], Gianpiero L Cavalleri[19,20], Fernando Cendes[8], Luis Concha[21], Esmaeil Davoodi-bojd[22], Patricia M Desmond[23], Orrin Devinsky[24], Colin P Doherty[25,26], Martin Domin[27], John S Duncan[28,29], Niels K Focke[30,31], Sonya F Foley[32], Antonio Gambardella[33,19], Ezequiel Gleichgerrcht[3], Renzo Guerrini[11], Khalid Hamandi[34,35], Akari Ishikawa[8], Simon S Keller[36,37], Peter V Kochunov[38], Raviteja Kotikalapudi[39], Barbara AK Kreilkamp[36,37], Patrick Kwan[40,41], Angelo Labate[33,17], Soenke Langner[42,43], Matteo Lenge[11,44] , Min Liu[45], Elaine Lui[46,23], Pascal Martin[31], Mario Mascalchi[47], José CV Moreira[8], Marcia E Morita-Sherman[8,48], Terence J O'Brien[40,41,49], Heath R Pardoe[50], José C Pariente[16], Letícia F Ribeiro[8], Mark P Richardson[51], Cristiane S Rocha[8], Raúl Rodríguez-Cruces[15,21], Felix Rosenow[52,53], Mariasavina Severino[54], Benjamin Sinclair[40,49], Hamid Soltanian-Zadeh[55,56], Pasquale Striano[57,58], Peter N Taylor[59], Rhys H Thomas[60,61], Domenico Tortora[54], Dennis Velakoulis[62,63], Annamaria Vezzani[64], Lucy Vivash[40,49], Felix von Podewils[65], Sjoerd B Vos[66,67], Bernd Weber[68], Gavin P Winston[69,70,67], Clarissa L Yasuda[8], Alyssa H Zhu[71], Paul M Thompson[71], Christopher D Whelan[6,72], Neda Jahanshad[71], Sanjay M Sisodiya[70,73], Carrie R McDonald[74]

**Affiliations**
[1]Department of Neurosciences, Center for Multimodal Imaging and Genetics, University of California San Diego, 9500 Gilman Dr, La Jolla 92093 CA, United States
[2]Center for Multimodal Imaging and Genetics, University of California San Diego, 9500 Gilman Dr, La Jolla 92093 CA, United States
[3]Department of Neurology, Medical University of South Carolina, 96 Jonathan Lucas St CSB 301 MSC 606, Charleston 29425 South Carolina, United States
[4]Maurice Wohl Clinical Neuroscience Institute, Institute of Psychiatry, Psychology & Neuroscience, Kings College London, 125 Coldharbour Lane, London SE5 9NU London, United Kingdom
[5]Neurology Department, Yale School of Medicine, 333 Cedar Street, New Haven 6510 Connecticut, USA
[6]Molecular and Cellular Therapeutics, the Royal College of Surgeons in Ireland, Dublin, Ireland

[7]Centre of Medical Image Computing, Department of Medical Physics and Biomedical Engineering, University College London, 90 High Holborn, London WC1V 6LJ NA, UK
[8]Department of Neurology, University of Campinas - UNICAMP, Rua Vital Brasil, 251, Campinas 13083-888 São Paulo, Brazil
[9]Center for Multimodal Imaging and Genetics, UCSD School of Medicine, 9452 Medical Center Dr, La Jolla 92037 CA, USA
[10]Boston University School of Medicine, 72 East Concord St, Boston 2118 MA, USA
[11]Pediatric Neurology, Neurogenetics and Neurobiology Unit and Laboratories, Children's Hospital A. Meyer-University of Florence, Florence, Italy, viale Pieraccini 24, Florence 50139, Italy
[12]USL Centro Toscana, Neurology Unit, Nuovo Ospedale Santo Stefano, Prato, Italy, via Suor Niccolina Infermiera 20, Prato 59100, Italy
[13]Department of Diagnostic and Interventional Neuroradiology, University Hospital Tübingen, Hoppe-Seyler-Straße 3, Tübingen 72076, Germany
[14]Neuroimaging of Epilepsy Laboratory, Montreal Neurological Institute, McGill University, 3801 University Street, Montreal H3A 2B4 Quebec, Canada
[15]Montreal Neurological Institute, McGill University, 3801 University Street, Montreal H3A2B4 Quebec, Canada
[16]Magnetic Resonance Image Core Facility, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Carrer del Rosselló, 153, Barcelona 8036 Barcelona, Spain
[17]Neuroscience Research Center, University Magna Graecia, viale Europa, Germaneto, 88100, Catanzaro, Italy
[18]Neuroscience, Institute of Psychiatry, Psychology and Neuroscience, De Crespigny Park, London SE5 8AF London, United Kingdom
[19]Royal College of Surgeons in Ireland, School of Pharmacy and Biomolecular Sciences, 123 St Stephens Green, Dublin D02 YN77 Dublin, Ireland
[20]FutureNeuro Research Centre, Science Foundation Ireland, 123 St Stephens Green, Dublin D02 YN77, Ireland
[21]Institute of Neurobiology, Universidad Nacional Autonoma de Mexico, Blvd. Juriquilla 3001, Queretaro 76230, Queretaro, Mexico
[22]Radiology and Research Administration, Henry Ford Hospital, 1 Ford Place, Detroit 48202 Michigan, United States
[23]Department of Radiology, Royal Melbourne Hospital, University of Melbourne, Grattan St, Melbourne 3050 Victoria, Australia
[24]Director, NYU Epilepsy Center, 223 E 34 St, New York 10016 New York, USA
[25]Division of Neurology, Trinity College Dublin, TBSI, Pearce Street, Dublin D02 R590 Dublin, Ireland
[26]FutureNeuro SFI Centre for Neurological Disease, RCSI, St Stephen's Green, Dublin D02 H903 Dublin, Ireland
[27]Functional Imaging Unit, University Medicine Greifswald, Walther-Rathenau-Str. 46, Greifswald 17475 M/V, Germany
[28]Department of Clinical and Experimental Epilepsy, UCL Queen Square Institute of Neurology, Queen Square, London WC1N 3BG, United Kingdom

[29]MRI Unit, Chalfont Centre for Epilepsy, Chesham Lane, Chalfont-St-Peter SL9 0RJ Bucks, United Kingdom
[30]Clinical Neurophysiology, University Medicine Göttingen, Robert-Koch-Str. 40, 37099 Göttingen , Germany
[31]Department of Epileptology, University of Tübingen, Hoppe-Seyler-Straße 3, 72076 Tübingen, Germany
[32]CUBRIC, Cardiff University, Maindy Road, Cardiff CF24 4HQ Cardiff, Wales
[33]Institute of Neurology, University Magna Graecia, viale Europa, 88100, Catanzaro, Italy
[34]The Wales Epilepsy Unit, Cardiff and Vale University Health Board, Cardiff CF144XW Cardiff, UK
[35]Brain Research Imaging Centre, Cardiff University, Maindy Road, Cardiff CF24 4HQ , UK
[36]Institute of Translational Medicine, University of Liverpool, Pembroke Place, Liverpool L69 3BX England, United Kingdom
[37]Walton Centre NHS Foundation Trust, Lower Lane, Liverpool L9 7LJ , United Kingdom
[39]Maryland Psychiatric Research Center, 55 Wade Ave, Baltimore 21228 MD, USA
[40]Department of Neuroscience, Central Clinical School, Monash University, 99 Commercial Road, Melbourne 3004 Victoria, Australia
[41]Department of Medicine, University of Melbourne, Royal Melbourne Hospital, Grattan Street, Parkville 3050 Victoria, Australia
[42]Institute for Diagnostic Radiology and Neuroradiology, Ernst Moritz Arndt University Greifswald Faculty of Medicine, Ferdinand-Sauerbruch-Str., Greifswald 17475 N/A, Germany
[43]Institute for Diagnostic and Interventional Radiology, Pediatric and Neuroradiology, Rostock University Medical Centre, Ernst-Heydemann-Str. 6, Rostock 18057 N/A, Germany
[44]Functional and Epilepsy Neurosurgery Unit, Children's Hospital A. Meyer-University of Florence, viale Pieraccini 24, Florence 50139 Florence, Italy
[45]Department of Neurology, Montreal Neurological Institute, 3801 University St, Montreal H3A 2B4 QC, Canada
[46]Department of Medicine and Radiology, University of Melbourne, 300 Grattan Street, Parkville 3050 Victoria, Australia
[47]Meyer Children Hospital University of Florence, Florence, Italy, Viale Pieraccini, Florence 50130 Tuscany, Italy
[48]Cleveland Clinic, 9500 Euclid Ave, Cleveland 44195 Ohio, United States
[49]Department of Neurology, Alfred Health, 56 Commercial Road, Melbourne 3004 Victoria, Australia
[50]Department of Neurology, New York University School of Medicine, 145 East 32nd St, New York City 10016 New York, United States
[51]Division of Neuroscience, King's College London, Institute of Psychiatry, London SE5 8AB N/A, United Kingdom
[52]Epilepsy Center Frankfurt Rhine-Main, University Hospital Frankfurt, Germany, Schleusenweg 2-16, Frankfurt 60528 Hesse, Germany
[53]Center for Personalized Translational Epilepsy Research (CePTER) , Goethe-University Frankfurt, Schleusenweg 2-16, Frankfurt a. M. 60528, Germany

[54]Neuroradiology Unit, IRCCS Istituto Giannina Gaslini, via Gaslini 5, Genoa 16147 Liguria, Italy
[55]Radiology and Research Administration, Henry Ford Health System, 1 Ford Place, Detroit 48202-2692 Michigan, United States
[56]School of Electrical and Computer Engineering, University of Tehran, North Kargar Ave., Tehran 14399-57131 Tehran, Iran
[57]IRCCS Istituto Giannina Gaslini, Via Gaslini, 5, Genoa 16147 Liguria, Italy
[58]Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genova, Genova, Italy
[59]School of Computing, Newcastle University, Urban Sciences Building, Science Square, Newcastle upon Tyne NE4 5TG Tyne & Wear, United Kingdom
[60]Translational and Clinical Research Institute, Newcastle University, Framlington Place, Newcastle upon Tyne NE2 4HH, United Kingdom
[61]Royal Victoria Infirmary, Victoria Road, Newcastle upon Tyne NE1 4LP, United Kingdom
[62]Royal Melbourne Hospital, 300 Grattan St, Melbourne 3050 Victoria, Australia
[68]University of Melbourne, Parkville, Melbourne 3050 Victoria, Australia
[63]Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Via Mario Negri 2, Milano 20156 Italy, Italy
[64]Epilepsy Center, University Medicine Greifswald, Sauerbruchstrafle 1, Greifswald 17489 Mecklenburg-Vorpommern, Germany
[65]Centre for Medical Image Computing, University College London, 90 High Holborn, 1st floor, London WC1V 6LJ London, United Kingdom
[66]Department of Clinical and Experimental Epilepsy, UCL Queen Square Institute of Neurology, Queen Square, London WC1N 3BG, United Kingdom
[67]Epilepsy Society, MRI Unit, Chalfont St Peter SL9 0RJ, Buckinghamshire, United Kingdom
[68]Institute of Experimental Epileptology and Cognition Research, University of Bonn, Venusberg Campus 1, Bonn 53127 NRW, Germany
[69]Department of Medicine, Division of Neurology, Queen's University, Kingston K7L 3N6 Ontario, Canada
[70]MRI Unit, Chalfont Centre for Epilepsy, Chesham Lane, Chalfont-St-Peter SL9 0RJ Bucks, United Kingdom
[71]Imaging Genetics Center, Mark & Mary Stevens Institute for Neuroimaging and Informatics, USC Keck School of Medicine, 2025 Zonal Avenue, Los Angeles 90232 CA, USA
[72]Research and Early Development (RED), Biogen Inc., Cambridge, MA, 02139, USA 90292, 4676 Admiralty Way Ste 200, Marina del Rey 90292-6601 California, United States
[73]Chalfont Centre for Epilepsy, Chesham Lane, Chalfont-St-Peter SL9 0RJ Bucks, United Kingdom
[74]Department of Psychiatry, Center for Multimodal Imaging and Genetics, University of California San Diego, 9500 Gilman Dr, La Jolla 92093 CA, United States

**Corresponding author**
Carrie R McDonald
camcdonald@health.ucsd.edu
(+1) 858-534-2678
Department of Psychiatry, Center for Multimodal Imaging and Genetics, University of California San Diego, 9500 Gilman Dr, La Jolla 92093 CA, United States

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## Abstract

The epilepsies are commonly accompanied by widespread abnormalities in cerebral white matter. ENIGMA-Epilepsy is a large quantitative brain imaging consortium, aggregating data to investigate patterns of neuroimaging abnormalities in common epilepsy syndromes, including temporal lobe epilepsy, extratemporal epilepsy, and genetic generalized epilepsy. Our goal was to rank the most robust white matter microstructural differences across and within syndromes in a multicentre sample of adult epilepsy patients. Diffusion-weighted MRI data were analyzed from 1,069 healthy controls and 1,249 patients: temporal lobe epilepsy with hippocampal sclerosis (N=599), temporal lobe epilepsy with normal MRI (N=275), genetic generalized epilepsy (N=182) and nonlesional extratemporal epilepsy (N=193). A harmonized protocol using tract-based spatial statistics was used to derive skeletonized maps of fractional anisotropy and mean diffusivity for each participant, and fiber tracts were segmented using a diffusion MRI atlas. Data were harmonized to correct for scanner-specific variations in diffusion measures using a batch-effect correction tool (ComBat). Analyses of covariance, adjusting for age and sex, examined differences between each epilepsy syndrome and controls for each white matter tract (Bonferroni corrected at $p<0.001$). Across *"all epilepsies"* lower fractional anisotropy was observed in most fiber tracts with small to medium effect sizes, especially in the corpus callosum, cingulum and external capsule. There were also less robust increases in mean diffusivity. Syndrome-specific fractional anisotropy and mean diffusivity differences were most pronounced in patients with hippocampal sclerosis in the ipsilateral parahippocampal cingulum and external capsule, with smaller effects across most other tracts. Individuals with temporal lobe epilepsy and normal MRI showed a similar pattern of greater ipsilateral than contralateral abnormalities, but less marked than those in patients with hippocampal sclerosis. Patients with generalized and extratemporal epilepsies had pronounced reductions in fractional anisotropy in the corpus callosum, corona radiata and external capsule,

and increased mean diffusivity of the anterior corona radiata. Earlier age of seizure onset and longer disease duration were associated with a greater extent of diffusion abnormalities in patients with hippocampal sclerosis. We demonstrate microstructural abnormalities across major association, commissural, and projection fibers in a large multicentre study of epilepsy. Overall, patients with epilepsy showed white matter abnormalities in the corpus callosum, cingulum and external capsule, with differing severity across epilepsy syndromes. These data further define the spectrum of white matter abnormalities in common epilepsy syndromes, yielding more detailed insights into pathological substrates that may explain cognitive and psychiatric co-morbidities and be used to guide biomarker studies of treatment outcomes and/or genetic research.

## Introduction

Epilepsy affects over 50 million people worldwide (Bell *et al.*, 2014). Focal epilepsies account for around 60% of all adult epilepsy cases, and temporal lobe epilepsy (TLE) is the most common (Téllez-Zenteno and Hernández-Ronquillo, 2012). TLE is associated with hippocampal sclerosis (HS) in 60-70% of cases (Coan and Cendes, 2013). Among adult epilepsy patients, up to 20% have genetic generalized epilepsy (GGE), with bilateral synchronous seizure onset and a presumed genetic background (Scheffer *et al.*, 2017). These epilepsy syndromes are frequently studied in isolation and may have distinct pathophysiological substrates and mechanisms. Their unique *and* shared biological pathways are beginning to be unraveled using population genetics (ILAE, 2018) and transcriptomics (Altmann *et al.*, 2017), paving the pathway for potential novel treatments.

Once considered primarily "gray matter" diseases, brain imaging studies with diffusion magnetic resonance imaging (dMRI) have helped reveal that both focal and generalized epilepsies represent network disorders with widespread white matter alterations even in the absence of visible MRI lesions (Engel *et al.*, 2013). Patients with TLE, particularly those with HS, may exhibit white matter abnormalities both proximal to and distant from the seizure focus, often most pronounced in the ipsilateral hemisphere (Focke *et al.*, 2008; Ahmadi *et al.*, 2009; Labate *et al.*, 2015; Caligiuri *et al.*, 2016). Studies in patients with GGE have demonstrated microstructural compromise in frontal and parietal regions bilaterally, and in thalamocortical pathways (Keller *et al.*, 2011; Lee *et al.*, 2014; Szaflarski *et al.*, 2016). White matter disruption in epilepsy is also linked to cognitive functioning (McDonald *et al.*, 2008; Yogarajah *et al.*, 2008, 2010) and postsurgical seizure outcomes (Bonilha *et al.*, 2015; Keller *et al.*, 2015, 2017; Gleichgerrcht *et al.*, 2018), indicating the importance of white matter networks in the pathophysiology and co-morbidities of epilepsy.

Meta-analyses and single-site studies of dMRI suggest widespread microstructural abnormalities in patients with focal epilepsy affecting association, commissural, and projection fibers, whereas microstructural differences in GGE are reportedly less pronounced (Otte *et al.*, 2012; Slinger *et al.*, 2016). Unfortunately, the exact tracts, spatial pattern, and extent of damage reported varies across studies, making it hard to draw conclusions about syndrome-specific and generalized white matter abnormalities in epilepsy. Inconsistencies may be due, in part, to small sample sizes at individual centers, which may lack power to detect reliable differences across a large number of white matter tracts and multiple diffusion measures. Methods for image acquisition, processing, and tract selection also differ greatly across studies, adding other sources of variability. Few studies consider white matter abnormalities as a function of sex, age, and key clinical characteristics leading to multiple uncertainties in the findings. Although meta-analyses reduce some of these limitations, harmonizing the image processing and data analysis in a consortia effort alleviates some of the known sources of variation and allows for the statistical modeling of other population differences. Furthermore, pooling raw data across a large number of centers in a *mega-analysis*[1] may offer greater power to detect group effects and enable cross-syndrome comparisons that have not previously been possible. Further, due to the collation of world-wide harmonized image analysis protocols, analysis, and reporting of results, white matter differences in epilepsy can now be directly compared to those of other neurological and psychiatric disorders, highlighting pathology that may be unique to epilepsy and/or its treatments.

Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) is a global initiative, combining individually collected samples from studies around the world into a

[1] A *meta-analysis* aggregates summary results (e.g. effect size estimates, standard errors, and confidence intervals) across studies, but a *mega-analysis* aggregates individual participant data across studies, and may allow additional data harmonization. For an empirical comparison between the two techniques using structural MRI data, please refer to Boedhoe *et al.*, 2018.

single large-scale study, with coordinated image processing, and integrating imaging, phenotypic, and genomic data from hundreds of research centers worldwide (Thompson *et al.*, 2020). Standardized protocols for image processing, quality assurance, and statistical analyses were applied using the validated ENIGMA-dMRI protocols for multi-site diffusion tensor imaging (DTI) harmonization, http://enigma.usc.edu/ongoing/dti-working-group/ (Jahanshad *et al.*, 2013; Kochunov *et al.*, 2014, 2015).

Our primary goal was to identify and rank the most robust white matter microstructural alterations across and within common epilepsy syndromes in a sample of 1,249 adult epilepsy patients and 1,069 healthy controls across nine countries from North and South America, Europe and Australia. First, we studed all patients in aggregate ("all epilepsies") compared to age and sex matched controls, followed by targeted analyses focusing on patients with right and left TLE-HS, right and left non-lesional TLE (TLE-NL), nonlesional extratemporal epilepsy (ExE), and GGE. We characterize effect size (ES) differences across *and* within these epilepsy syndromes in fractional anisotropy (FA) and mean diffusivity (MD), as well as axial (AD) and radial (RD) diffusivity. We also examine regional white matter associations with age of seizure onset and disease duration.

We hypothesized that, compared to controls, each patient group would show white matter alterations beyond the suspected epileptogenic region, with unique patterns in each group. Specifically, we hypothesized that patients with TLE would show the most pronounced alterations in ipsilateral temporo-limbic regions, most notably in TLE-HS. We hypothesized that patients with GGE would show bilateral fronto-thalamocortical alterations. We also hypothesized that common white matter alterations would emerge across the patient groups and that many of these regional alterations would correlate with years of disease duration.

## Materials and methods

All study participants provided written informed consent for the local study, and the local institutional review boards and ethics committees approved each included cohort study.

## Study sample

This study from the ENIGMA-Epilepsy working group consists of 21 cohorts from nine different countries and includes dMRI scans from 1,069 healthy controls and 1,249 adult epilepsy patients. Demographic and clinical characteristics of the samples are presented in Table 1 (by site) and Table 2 (across site). An epilepsy specialist assessed seizure and syndrome classifications at each center, using the International League Against Epilepsy (ILAE) criteria. For the TLE subgroups, we included anyone with the typical electroclinical constellation of this syndrome (Berg *et al.*, 2010). All TLE-HS patients had a neuroradiologically-confirmed diagnosis of unilateral hippocampal atrophy and increased T2 signal on clinical MRI, whereas all of the TLE-NL patients had a normal MRI undertaken at the same time as the analyzed dMRI scan. Participants with a normal MRI and frontal, occipital, or parietal epilepsy were labelled as ExE. Participants with tonic-clonic, absence or myoclonic seizures with generalized spike-wave discharges on EEG were included in the GGE group. Data on anti-epilepsy drug (AED) regimen, seizure frequency, and clinical outcomes (e.g., drug resistance, postsurgical outcome) were not available at the time of the analysis. We excluded participants who did not meet criteria for one of the above epilepsy syndromes or who had MRI-visible lesions that would disrupt brain morphometry, including malformations of cortical development, tumors or prior neurosurgery. Participants were between 18 and 70 years of age.

## Image processing and analysis

Scanner descriptions and acquisition protocols for all sites are provided in Supplementary Table 1. Individual scanners that used different acquisition protocols are listed as separate scanner instances. Each site conducted the preprocessing of diffusion-weighted images, including eddy current correction, echo-planar imaging (EPI)-induced distortion correction, and tensor estimation. Next, diffusion-tensor imaging (DTI) images were processed using the ENIGMA-DTI protocols. These image processing and quality control protocols are freely available at the ENIGMA-DTI (http://enigma.ini.usc.edu/ongoing/dti-working-group/) and NITRC (https://www.nitrc.org/projects/enigma_dti/) webpages. Measures of FA, MD, AD and RD were obtained for 38 regions of interest using the Johns Hopkins University (JHU) atlas (Figure 1).

For analyses of all patients and for each syndrome, we used the left and right tracts, the midline structures of the body (BCC), genu (GCC), and splenium (SCC) of the corpus callosum and the average diffusion metric (FA/MD/AD/RD) across the whole brain (38 ROIs). Corrections for multiple comparisons were carried out for each epilepsy syndrome, based on the number of ROIs: 34 bilateral white matter regions + BCC + GCC + SCC + Average FA=38 ROIs: Bonferroni-corrected threshold for significance p=0.05/38=0.001.

## Data harmonization

The batch-effect correction tool, ComBat, was used to harmonize between-site and between-protocol variations in diffusion metrics as previously demonstrated (Fortin *et al.*, 2017). The method globally rescales the data (all ROIs for FA, MD, RD or AD separately) for each scanner instance using a z-score transformation map common to all features. ComBat uses an empirical Bayes framework (Johnson *et al.*, 2007) to improve the variance

of the parameter estimates, assuming that all ROIs share the same common distribution. Thus, all ROIs are used to inform the statistical properties of the scanner effects. We set each scanner instance as each individual scanner used in the collection of MR exams, and where there were different scanning protocols used on the same scanner, each protocol was set as a different scanning instance. Scanner type was used as the batch effect and diagnosis (patients versus controls) and syndrome (GGE, TLE-HS, TLE-NL, and ExE) were used as the biological phenotypes of interest. This technique has been recently applied in other ENIGMA DTI investigations of brain disorders (Villalón-Reina *et al.*, 2019; Zavaliangos-Petropulu *et al.*, 2019).

## Statistical analysis

Statistical analysis was performed in the Statistical Package for the Social Sciences (SPSS v26.0). Pearson correlation examined the association between age of onset and disease duration. Analysis of variance (ANOVA) was used to test for differences in demographic and clinical characteristics among the epilepsy syndromes. To test for differences between syndromes and controls and to test for global effects of age at scan and sex on white matter, multivariate analysis of covariance (MANCOVA) was performed per diffusion metric, adjusting for age, age$^2$ and sex. Age$^2$ was included in all analyses to model the non-linear effects of age on diffusivity measures (Lebel *et al.*, 2012). ANCOVAs were then performed of each patient syndrome compared to controls controlling for age, age$^2$ and sex and Bonferroni corrected at $p<0.001$. Cohen's *d* effect sizes (ES) were calculated for each right and left fiber tract between controls and each patient syndrome based on the estimated marginal means (adjusted for age, age$^2$, and sex) and interpreted according to the following criteria: *small d=0.20-0.49 ; medium d=0.50-0.79; large d>=0.80* (Sawilowsky, 2008). Throughout the text and figures, positive ES values correspond to patients having higher

values than controls, whereas negative ES values correspond to patients having lower values relative to controls. Partial correlations controlling for the same covariates were performed to evaluate the relationship between each fiber tract FA/MD and age of seizure onset and disease duration (corrected $p<0.001$). To demonstrate the most robust group differences, only tracts that showed medium and large effects are described in the text. Tracts with small effects are detailed in the Supplementary materials (see Supplementary materials for all results: Tables 4-7 and Figs. 1-2). In followup analysis to check that heteroscedasticity was not influencing results, FSL PALM (Winkler *et al.*, 2014) was used to test if permutation testing of the difference in FA between patients and controls was similar to the core ANCOVA results (Fig. 3, Supplementary Table 4). The model controlled for age and sex and 10000 permutations were run with exchangability blocks (Winkler *et al.*, 2015) set for permutations to take place within scanner instances only. We used the Aspin-Welch *v* test statistic and the simulated significance P(sim) threshold was set at $p< 0.001$.

## Results

# Demographics

Demographic and clinical characteristics of each sample are presented in Table 2. A one-way ANOVA with group as the between-subjects factor revealed differences across the seven groups in age [$F(6, 2083) = 13.3$, $p<0.001$)]. Two, one-way ANOVAs across the six patient syndromes revealed group differences in age of seizure onset [$F(5, 1095) = 6.3$, $p<0.001$] and disease duration [$F(5,1039) = 22.4$, $p<0.001$]. Post-hoc comparisons revealed that controls were younger than both TLE-HS groups and older than patients with GGE and ExE (all p-values<0.05). Both TLE-HS groups and the left TLE-NL group were older than the GGE and ExE groups ($p<0.05$). The right TLE-HS group was older than both TLE-NL groups ($p<0.05$). The GGE and TLE-HS groups had an earlier age of seizure onset than the TLE-NL groups. Duration of illness in TLE-HS groups was longer than in all other groups.

# Data harmonization with ComBat

Initial frequency plots revealed high variability in the distribution of diffusivity measures (e.g., mean FA, mean MD) among scanner instances (Fig. 2A). After batch correction with ComBat, the distributions were centered around a common mean (Fig. 2B), but maintained their expected association with age (Fig. 2C). Following this process, extreme ROI outliers beyond 3 SD were removed from the subsequent analysis (i.e., per ROI for a given subject, not per subject). This approach resulted in the removal of only 1-5 ROIs per site, per diffusion parameter. The harmonization process successfully reduced the variance of diffusivity measures, especially in MD, AD and RD (Supplementary Table 2).

# All epilepsies group

### Multivariate tests of within-subject effects

Comparing the whole epilepsy group with healthy controls, significant differences were observed in FA ($F$(228,13452)=4.7, $p$<0.001, Pillai's Trace=0.44, partial $\eta^2$=0.07), MD ($F$(228,11688)=2.8, $p$<0.001, Pillai's Trace=0.31, partial $\eta^2$=0.05), RD ($F$(228,11790)=3.28, $p$<0.001, Pillai's Trace=0.36, partial $\eta^2$=0.06), and AD ($F$(228,11946)=1.96, $p$<0.001, Pillai's Trace=0.22, partial $\eta^2$=0.04). Sex, age, and age$^2$ all significantly contributed to the model (see Supplementary Table 3). Compared to females, males generally had higher FA, slightly higher RD and no difference in MD or AD.

### All epilepsies vs healthy controls

The "all epilepsies" group showed lower FA than controls globally in 36 of 38 ROIs ($p$<0.001; Fig. 3, Supplementary Table 4), with medium ES observed for the Average FA ($d$=-0.71), external capsule (EC; left $d$=-0.64, right $d$=-0.63), body ($d$=-0.59) and genu ($d$=-0.59) of the corpus callosum (BCC and GCC), cingulate gyrus of the cingulum bundle (CGC, left $d$=-0.57, right $d$=-0.50), sagittal stratum (SS, left $d$=0.55, right $d$=0.52), anterior corona radiata (ACR, left $d$=-0.50, right $d$=-0.52), and left parahippocampal cingulum (CGH, $d$=-0.52). Followup permutation testing confirmed that the same ROIs were significantly lower in FA in patients compared to controls when accounting for possible heteroscedasticity between scanner instances (Supplementary Table 16).

The "all epilepsies" group showed higher MD than the controls in 27 ROIs (Fig. 4, Supplementary Table 5). Similar to the MD, patients showed higher RD in 34 ROIs (Supplementary Fig. 1, Supplementary Table 6) with a medium-sized effect seen in the right EC ($d$=0.52). Higher AD was observed in 8 ROIs (Supplementary Fig. 2, Supplementary Table 7).

### Age of onset and disease duration

Earlier age of seizure onset was significantly correlated (all *p-values* <.001) with longer disease duration across all patients ($r$=-0.58) and within each syndrome: GGE ($r$=-0.39), left TLE-HS ($r$=-0.65), right TLE-HS ($r$=-0.66), left TLE-NL ($r$=-0.57), right TLE-NL ($r$=-0.54), and ExE ($r$=-0.54).

Across all epilepsy patients, earlier age of onset was associated with lower FA across 28 ROIs ($r$=0.1 to 0.3, $p$<0.001), higher MD in 16 ROIs, and higher RD in 28 ROIs (Supplementary Tables 8, 10, 12). The most robust associations were observed between an earlier age of seizure onset and lower FA in the Average FA, GCC, and bilateral EC, and CGC (r's between 0.16 and 0.19). There were no significant relationships between age of onset and AD in the "all epilepsies" group (Supplementary Table 14).

Across all epilepsy patients, disease duration showed significant associations with diffusivity measures (Supplementary Tables 9, 11, 13, 15). A longer disease duration was associated with lower FA in 14 ROIs, increased MD in 9 ROIs, and increased RD in 27 ROIs. Of note, longer disease duration was associated with lower FA in BCC, CGC, and EC, and with lower Average FA (r's = -0.15 to -0.17). There were no significant relationships between disease duration and AD in all patients.

## TLE-HS group

### TLE-HS patients vs healthy controls

Left TLE-HS patients ($n$=319) showed significantly lower FA than controls in 35 of 38 ROIs (Fig. 3, Supplementary Table 4), with large ES differences in the left EC ($d$=-1.02), left CGH ($d$=-1.01), Average FA ($d$=-0.92), left CGC ($d$=-0.89), and left fornix/stria terminalis (FXST, $d$=-0.83).

Medium-sized effects were observed in GCC (*d*=-0.79), left SS (*d*=-0.78), BCC (*d*=-0.75), right CGC (*d*=-0.68), right EC (*d*=-0.68), left superior longitudinal fasciculus (SLF, *d*=-0.67), left ACR (*d*=-0.66), left anterior limb of the internal capsule (ALIC, *d*=-0.61), left retrolenticular portion of the internal capsule (RLIC, *d*=-0.61), left uncinate (UNC, *d*=-0.61), right SLF (*d*=-0.58), left PCR (*d*=-0.54), right ACR (*d*=-0.53), and right SS (*d*=-0.52).

Significantly higher MD was observed in 28 ROIs (Fig. 4, Supplementary Table 5), with medium-sized effects in the left EC (*d*=0.69), left SS (*d*=0.66), and average MD (*d*=0.55). Left TLE-HS patients showed significantly higher RD in 33 of 38 ROIs (Supplementary Fig. 1, Supplementary Table 6). A large effect of higher RD was observed for the left EC (*d*=0.83), and medium-sized effects were seen for the left SS (*d*=0.79), left CGC (*d*=0.69), left CGH (*d*=0.67), average RD (*d*=0.66), right EC (*d*=0.61), left FXST (*d*=0.59), left ACR (*d*=0.57), SLF (left *d*=0.56, right *d*=0.53), right ACR (*d*=0.52), and left RLIC (*d*=0.51). Higher AD was observed in five ROIs (Supplementary Figure 2, Supplementary Table 7).

Right TLE-HS patients (*n*=280) showed lower FA than controls in 26 of 38 ROIs ($p<0.001$; Fig. 3, Supplementary Table 4), with large effects observed for the average FA (*d*=-1.06), right CGH (*d*=-1.02), right EC (*d*=-0.99), right UNC (*d*=-0.90), BCC (*d*=-0.87), GCC (*d*=-0.85) and right SS (*d*=-0.83). Medium-sized effects were observed in the right ACR (*d*=-0.78), right CGC (*d*=-0.73), left EC (*d*=-0.68), left ACR (*d*=-0.68), left CGC (*d*=-0.68), left tapetum (TAP, *d*=-0.68), right PTR (*d*=-0.62), right FX/ST (*d*=-0.61), right SLF (*d*=-0.59), right TAP (*d*=-0.59), right ALIC (*d*=-0.55), right PCR (*d*=-0.55), left SS (*d*=-0.55), and left SCR (*d*=-0.53).

Higher MD in the patient group were observed in 23 ROIs (Fig. 4, Supplementary Table 5), with medium-sized effects shown in the right SS (*d*=0.67), right EC (*d*=0.62), right UNC (*d*=0.62), average MD (*d*=0.60) and right ACR (*d*=0.59). Significantly higher RD in the

patient group were observed in 31 ROIs (Supplementary Figure 1, Supplementary Table 6), with a large effect observed for the right EC (*d*=0.84), and medium effects seen for the right SS (*d*=0.76), right UNC (*d*=0.72), average RD (*d*=0.70), right ACR (*d*=0.69), left EC (*d*=0.63), right SLF (*d*=0.62), right CGH (*d*=0.61), right CGC (*d*=0.57), BCC (*d*=0.56), right FX/ST (*d*=0.52), and left ACR (*d*=0.51). Higher AD was observed in six ROIs (Supplementary Figure 2, Supplementary Table 7).

**Age of onset and disease duration**

For left TLE-HS, earlier age of onset was associated with lower FA in 4 ROIs, including the Average FA, BCC, GCC, and left EC. Earlier age of seizure onset was associated with higher RD in 2 ROIs (Supplementary Tables 8, 12). There was no detected relationship between age of onset and either MD or AD in the left TLE-HS group (Supplementary Tables 10, 14).

For right TLE-HS, earlier age of onset was related to lower FA across 9 ROIs, including the Average FA, BCC, SCC, right EC, left and right CGH, right PCR, and right SLF, increased MD in 7 ROIs, and increased RD in 7 ROIs (Supplementary Tables 8, 10, 12). There was no detected relationship between age of onset and AD in the TLE-HS groups (Supplementary Table 14).

For left TLE-HS patients, longer disease duration was associated with lower FA in four ROIs (BCC, bilateral CGC, and left EC) and higher RD in one ROI (left SS). There were no significant relationships between disease duration and MD or AD (Supplementary Tables 9, 11, 13, 15). For right TLE-HS, longer disease duration was associated with lower FA in 8 ROIs (Average FA and SCC, bilateral TAP, and right CGH, EC, PCR, and UNC), higher MD in six ROIs, and higher RD in 10 ROIs.

# TLE-NL group

### TLE-NL vs healthy controls

The left TLE-NL patients ($n$=162) showed lower FA than controls in 20 ROIs (Fig. 3, Supplementary Table 4), higher MD in one ROI (Fig. 4, Supplementary Table 5), and higher RD in 6 ROIs (Supplementary Figure 1, Supplementary Table 6). No significant effects of AD were detected (Supplementary Figure 2, Supplementary Table 7).

Right TLE-NL patients ($n$ = 113) showed significantly lower FA than controls in 19 ROIs ($p<0.001$; Fig. 3, Supplementary Table 4), with medium-sized effects observed in the right EC ($d$=-0.64), right SS ($d$=-0.60), Average FA ($d$=-0.58), right CGH ($d$=-0.55), right CGC ($d$=-0.51) and right UNC ($d$=-0.50). MD was increased in three ROIs ($p<0.001$, Fig. 4, Supplementary Table 5), specifically the right EC ($d$=0.46), right UNC ($d$=0.42) and right SS ($d$=0.42). Significantly higher RD was observed in 4 ROIs (Supplementary Figure 1, Supplementary Table 6), with a medium-sized effect shown in the right EC ($d$=0.50). No significant effects of AD were detected (Supplementary Figure 2, Supplementary Table 7).

### Age of onset and disease duration

For left TLE-NL, no diffusivity measure was associated with earlier age of onset or duration of illness (Supplementary Tables 8-15).

For right TLE-NL patients, younger age of onset and was related to lower FA in the right UNC ($r$=0.30, $p$<0.001), but not MD, AD, or RD (Supplementary Tables 8, 10, 12, 14). Disease duration was also associated with decreased FA in the right UNC ($r$= =-0.37, $p$<0.001), but not MD, AD, or RD (Supplementary Tables 9, 11, 13, 15).

# GGE group

### GGE patients vs healthy controls

GGE patients (n=113) showed significantly lower FA than controls in 28 ROIs ($p$<0.001; Fig. 3, Supplementary Table 4), with medium-sized effects observed in the GCC ($d$=-0.57), left SLF ($d$=-0.57), left EC ($d$=-0.55), left RLIC ($d$=-0.51), right SLF ($d$=-0.51) and left PCR ($d$=-0.50). GGE patients showed higher RD in 4 ROIs ($p$<0.001, Supplementary Fig. 1, Supplementary Table 6). No significant effects were seen for MD or AD (Fig. 4, Supplementary Fig. 2, Supplementary Tables 5, 7).

### Age of onset and disease duration

For GGE patients, there was no significant association between diffusivity measures and either age of onset of epilepsy or its duration.

# ExE group

### ExE patients vs healthy controls

ExE patients ($n$=193) showed significantly lower FA than controls in 33 ROIs ($p$<0.001; Fig. 1, Supplementary Table 4), with medium-sized effects observed for Average FA ($d$=-0.75), BCC ($d$=-0.65), GCC ($d$=-0.64), right ACR ($d$=-0.63), bilateral EC (left $d$=-0.60, right $d$=-0.58), left ALIC ($d$=-0.57), left ACR ($d$=-0.55), and right SS ($d$=-0.51). Higher MD was observed in 6 ROIs ($p$<0.001, Fig. 4, Supplementary Table 5) and RD in 22 ROIs ($p$<0.001, Supplementary Figure 1, Supplementary Table 6). No significant effects were seen in AD (Supplementary Figure 2, Supplementary Table 7).

### Age of onset and disease duration

For ExE patients, there were no significant associations between diffusivity measures and either age of onset of epilepsy, or its duration.

## Cross-syndrome comparisons

Post-hoc comparisons were conducted across the syndromes in the five ROIs that showed the largest ES in the "all epilepsies" analysis, namely Average FA/MD, ACR, BCC, CGC, and EC averaged across hemispheres (Figure 5). ANCOVAs, adjusting for age, age$^2$, sex, age of seizure onset, and disease duration revealed significant group differences in Average FA [$F$ (5, 874) = 3.8, $p$<0.05], as well as FA of the CGC [$F$(5, 874) = 5.0, $p$<0.05] and EC [$F$(5, 874) = 5.8, $p$<0.05].

There were differences across syndromes for the Average MD [$F$(5, 874) = 5.3, $p$<.05], ACR [$F$(5, 874) = 3.8, $p$<0.05], BCC [$F$(5, 874) = 4.9, $p$<0.05], CGC [$F$(5, 874) = 4.2, $p$<0.05], and the EC [$F$(5, 874) = 6.2, $p$<0.05]. Patients with left and right TLE-HS generally showed lower FA and higher MD than TLE-NL patients, as well as lower FA/higher MD than GGEs in CGC and the EC. The nonlesional groups (GGE, TLE-NL, and ExE) did not differ from one another.

## Comparisons with other disorders

Given the many common white matter FA differences observed across epilepsy syndromes, the question arises as to whether these effects are specific to epilepsy or also seen with other brain disorders. Figure 6 displays ES differences observed in the "all epilepsies" group (n=1,249) relative to findings from four other ENIGMA working groups: schizophrenia (SCZ; n=1,984; mean age, 36.2; 67% men), 22q11 syndrome (n=334; mean age, 16.9; 54% men), bipolar disorder (BP; n=1,482; mean age, 39.6; 39.3% men), and major

depressive disorder (MDD; n=921; mean age, 40.7; 39% men). The magnitude of the ESs were typically larger in epilepsy, compared to the other disorders for most white matter regions. Across the white matter regions, ESs in patients with epilepsy were significantly correlated with those in patients with BP (Spearman's rho $r$=0.53, $p$<0.05), SCZ ($r$=0.53, $p$<0.05), and MDD ($r$=0.44, $p$<0.05).

## Approach for multiple comparisons correction

Regional differences in diffusion parameters between syndromes and healthy controls were expressed as ESs (Cohen's d). In order to identify significant differences we adopted a Bonferroni correction that adjusted for testing 38 ROIs for each syndrome ($p$<0.001). However, an even more conservative approach corrects for each of the four diffusion metrics across the seven epilepsy syndromes. Implementing this very conservative Bonferroni cutoff would result in a threshold of $p$<0.05/(38*7*4)=4.7e-05. The combination of the large sample size and the observed medium to large effect sizes in the study results in most regional differences remaining significant even at the very conservative p-value threshold. However, in contrasts involving a smaller number of patients (controls compared to, e.g., GGE or TLE-NL) more regions would lose the "significant" label due to the reduced statistical power. Despite these few exceptions, the exact $p$-value cutoff does not alter the main finding that there were widespread white matter abnormalities across epilepsy syndromes. We report all effect sizes and $p$-values in the supplementary material for researchers interested to examine these results with alternate definitions of statistical significance.

## Discussion

This multi-site DTI study in epilepsy compared data from 1,249 patients with common epilepsy syndromes to 1,069 healthy controls. Data were acquired at 21 sites across North America, South America, Europe, and Australia and harmonized using the same post-processing pipeline and batch effect harmonization tool.

Our results reveal marked white matter alterations across epilepsy syndromes compared to controls, with varying magnitude of FA reduction and increased MD and RD. Effects were pronounced in patients with TLE-HS and modest in GGE. In TLE-HS, the greatest changes were seen ipsilateral to the seizure focus, implying a local effect. Notably, the magnitude of the diffusion changes was greater in epilepsy than that seen in SCZ, BP and MDD. The biological basis of reduced FA is considered primarily loss of axons and myelin sheaths, with increased RD and MD reflecting myelin disruption and increased extracellular space (Arfanakis *et al.*, 2002; Concha *et al.*, 2009). This raises the critical question of whether these diffusion abnormalities reflect the underlying pathologies that predispose to epilepsy, or if they are the consequence of epilepsy and are a biomarker of secondary damage. Since changes were more pronounced in those with a younger age of onset and longer duration of epilepsy, we hypothesize that the white matter changes represent likely secondary effects rather than being causal. However, a prospective longitudinal study of individuals from diagnosis onward is needed to answer this question.

Although previous studies have investigated white matter alterations *within* a specific epilepsy syndrome, our study is the first to include a diverse aggregation of epilepsy syndromes and address the question of shared brain alterations *across* syndromes. This analysis revealed widespread reductions in FA across most association, commissural, and projection fibers bilaterally, with smaller effects of increased MD. The most robust

alterations were observed in frontocentral regions, including the *genu* and body of the CC, ACR, CGC, and EC. These regional changes mirror results from our structural MRI findings (Whelan *et al.*, 2018), which revealed subcortical atrophy and neocortical thinning in fronto-central, midline structures, including the thalamus, pallidum, pre- and post central gyri, and superior frontal regions bilaterally. These regions showed the strongest association with both age of seizure onset and disease duration. Therefore, white matter abnormalities in these regions may be a result of both aberrant developmental (i.e., disruptions of late-myelinating pathways due to seizures; (Lee *et al.*, 2013; Ostrowski *et al.*, 2019) and degenerative (i.e., demyelination and/or axonal loss due to years of epilepsy, recurrent seizures, exposure to AEDs; (Günbey *et al.*, 2011)) processes. Although lower FA and higher MD have been interpreted as reflecting a combination of pathological processes, we observed differences across syndromes to be driven primarily by higher RD supporting the concept that disrupted or altered myelin, rather than significant axonal loss, may underlie these changes (Arfanakis *et al.*, 2002; Song *et al.*, 2002; Concha *et al.*, 2009).

## Temporal Lobe Epilepsy

A recent imaging-based meta-analysis (Slinger *et al.*, 2016) found that patients with TLE had pronounced and widespread white matter injury relative to other patient syndromes. We found that this pattern was much more robust and ipsilateral in patients with HS, particularly in hippocampal afferent and efferent tracts, including the CGH, FX/ST, and UNC. The proximity of these latter white matter regions to the epileptogenic zone, with changes being greater ipsilaterally than contralaterally, implies that these alterations are driven by intrinsic factors specific to the TLE-HS syndrome rather than long-term effects of AEDs. Contrary to prior work (Ahmadi *et al.*, 2009; Whelan *et al.*, 2018), we did not find

greater abnormalities in patients with left TLE relative to right TLE in either the TLE-HS or TLE-NL groups, nor did we find greater injury in males with TLE relative to females. Rather, men with TLE-HS and TLE-NL showed higher global FA values relative to women. This contrasts with a previous meta-analysis that found men with focal epilepsy to be more vulnerable to white matter injury relative to women (Slinger *et al.*, 2016). These findings do not appear to reflect differences in age, age of seizure onset, or disease duration, as these characteristics did not differ between men and women in our TLE cohorts. It has been reported that compared to age-matched women, men have greater white matter volume and neuronal number with fewer neuronal processes (Rabinowicz *et al.*, 1999), which is hypothesized to represent fewer, thicker and more organized fibers in men compared to more crossing fiber tracts in women (Schmithorst *et al.*, 2008). This hypothesis is supported by the finding that higher FA in males compared to females was also observed in our healthy control sample.

Patients with TLE-NL showed a very mild pattern of white matter disruption compared to TLE-HS (Campos *et al.*, 2015) (Fig. 3 and 4). Although this may, in part, reflect the greater likelihood for patients with TLE-NL to have a milder form of epilepsy, previous studies have shown that even among drug-resistant TLE, patients with TLE-NL harbor less severe cortical (Bernhardt *et al.*, 2016, 2019) and white matter (Liu *et al.*, 2012) abnormalities compared to TLE-HS. White matter disruptions in TLE-NL were notable in the EC and SS, both of which contain long-range association pathways. In particular, the SS contains fibers of the inferior fronto-occipital fasciculus and the inferior longitudinal fasciculus (Goga *et al.*, 2015). These fibers course through the temporal lobe lateral to the CGH and FX/ST supporting data suggesting that TLE-HS and TLE-NL involve different epileptogenic networks (Zaveri *et al.*, 2001; Mueller *et al.*, 2009). However, many FA/MD alterations did not differ between TLE-HS and TLE-NL patients, once age of seizure onset

and disease duration were taken into account (Fig. 5). Thus, the magnitude of these differences appears to be influenced by differences in clinical characteristics. This is supported by the association of an earlier age of seizure onset and longer disease duration with regional white matter disruption in TLE-HS, but not in TLE-NL.

## Genetic generalized epilepsy

GGE includes several related syndromes, defined electrographically by generalized, bisynchronous, and symmetric activity with spike-wave or polyspike-wave discharges (Weir, 1965; Seneviratne *et al.*, 2012). These syndromes have traditionally been associated with thalamocortical dysfunction, with some studies reporting atrophy in the thalamus (Whelan *et al.*, 2018) or thalamocortical networks (Bernhardt *et al.*, 2009), and other studies reporting no structural changes relative to controls (McGill *et al.*, 2014). Although patients with GGE showed modest alterations relative to patients with focal epilepsy across most fibers, these differences were broader than those previously observed (Slinger *et al.*, 2016) and include commissural (GCC), projection (ACR) and corticocortical association pathways (EC, SLF). In addition, the magnitude of these changes in the ACR was similar to those observed in other epilepsy syndromes after adjusting for clinical and demographic characteristics (Fig. 5). The ACR is part of the limbic-thalamo-cortical circuitry and includes thalamic projections from the internal capsule to the cortex, including prominent connections to the frontal lobe bilaterally (Catani *et al.*, 2002; Wakana *et al.*, 2004). Thus, degradation of these projection fibers supports the hypothesis that frontothalamic pathology is present in patients with GGE, including juvenile myoclonic epilepsy (JME) (Woermann *et al.*, 1999; Keller *et al.*, 2011).

## Extratemporal epilepsy

The group of patients with non-lesional focal ExE showed the most marked alterations in the BCC, GCC, ACR, CGC, and EC, and showed a similar pattern to the GGE group of bilateral fronto-central alterations. As frontal lobe epilepsy is the second most common type of focal epilepsy (Manford *et al.*, 1992), it is likely that this group dominated the ExE group, explaining the predominance of fronto-midline pathology. Unlike the TLE-HS, neither age of seizure onset nor disease duration were associated with regional white matter compromise. This may be related to the heterogeneity of this patient group, their later age of seizure onset and/or the fact that this non-lesional group may represent a "mild" form of ExE.

## Summary

In summary, we found shared white matter compromise across epilepsy syndromes, dominated by regional alterations in bilateral midline, fiber bundles. The question arises as to whether these shared alterations are specific to epilepsy or are non-specific effects of a chronic brain disorder. Comparison of our ES to those of five other ENIGMA populations revealed that the pattern of microstructural compromise in epilepsy was similar to, but more robust than, the patterns observed in BP, SCZ, and MDD. In particular, the CC body and genu were commonly affected across disorders, suggesting that microstructural compromise could reflect a shared patho-physiological mechanism. However, patients with epilepsy tend to have high rates of comorbid mood disorder (Kanner, 2006) and these were not characterized in our epilepsy sample. Therefore, overlap in white matter changes between our epilepsy cohort and major neuropsychiatric disorders could reflect the presence of comorbid psychiatric symptoms in our patients. Increasing evidence suggests that neuropsychiatric disorders themselves are not separated by sharp neurobiological boundaries (Baker *et al.*,

2019), but have overlapping of genetic influences and brain dysfunction (Brainstorm Consortium *et al.*, 2018; Radonjić *et al.*, 2019). Although genetic overlap between these neuropsychiatric disorders and epilepsy is low, overlap in dysfunctional brain networks may be partly due to comorbidities, and warrants further investigation.

## Limitations

First, although much effort was taken to apply post-acquisition harmonization, each scanner varied in either its image acquisition protocol or scanner hardware, or both, which increased methodological heterogeneity. Conversely, our results can be considered independent of any specific acquisition scheme, head coil or scanner model. Accordingly, while the absence of a single, standardized MR protocol incorporates scanner variance into the data, it also provides breadth that enhances the generalizability of findings. Due to the fact that some sites had a small sample of patients within a particular syndrome or no control data, we were unable to adequately implement statistical approaches that could specifically address site/sample bias. The statistical batch normalization process ComBat corrected differences between scanner instances, but may not adequately accommodate the heterogeneous neuropathology of epilepsy, resulting in a 'smoothing out' of differences between syndromes.

A second limitation is the challenge of directly ascribing lower FA and higher MD to demyelination and/or axonal injury. Specifically, lower FA can reflect the effects of crossing fibers, increases in extracellular diffusion (e.g., inflammation, edema) or other technical or biological factors. Therefore, advanced diffusion sequences such as high angular resolution diffusion imaging and multishell dMRI acquisitions, together with analysis of quantitative contrasts sensitive to tissue microstructural features and neuropathological investigations, would help better unravel the biological underpinnings of our findings.

The GGE and ExE subgroups represented heterogeneous cohorts, which may have contributed to the weaker effects noted in these groups relative to TLE-HS. Although we were underpowered in this study to divide our GGE and ExE patients into more specific syndromes, future studies of more targeted syndromes (i.e., JME) would be beneficial. Similarly, although all of the patients in our study were diagnosed according to ILAE guidelines, many patients did not receive intracranial EEG (iEEG). In practice, only a very small proportion of people with epilepsy ever have iEEG. Therefore, we cannot rule out the possibility that some patients were misclassified or had multi-focal seizure onsets that were not detected. The lack of iEEG and postoperative outcome data on all participants also made it challenging to further characterize our ExE patients according to seizure laterality or more specific seizure onset, or to confirm that our TLE-NL group did not include patients with seizure arising from other locations. Furthermore, the lack of clinical data prevented us from directly assessing how these diffusional changes were associated with specific AED regimens, comorbid disorders, cognitive performances, or how they relate to clinical outcomes (i.e., drug resistance or post-operative seizure outcome). These data are now being collected across the consortium to better characterize patients and evaluate the clinical utility of identifying syndrome-specific and shared microstructural injury in epilepsy.

## Conclusions and Clinical Implications

In the largest DTI mega-analysis of epilepsy, we demonstrate a pattern of robust white matter alterations within and across patient syndromes, revealing shared and unique features for each syndrome. These patterns of white matter injury may help to explain cognitive impairments associated with each syndrome [e.g., the extent of memory impairment in TLE has been linked to the extent of CGH and UNC damage (McDonald *et al.*, 2008)], as well as across syndrome similarities in cognitive profiles [e.g., patients with

TLE and GGE both present with executive dysfunction that may reflect their shared fronto-central white matter damage; (Abarrategui *et al.*, 2018; Reyes *et al.*, 2018)]. The extent of microstructural injury may also help to predict postsurgical seizure (Bonilha *et al.*, 2015) and cognitive (McDonald *et al.*, 2014) outcomes, or to inform which patients will respond to AEDs (Park *et al.*, 2020). Finally, cross-syndrome and cross-disease comparisons could help to inform gene expression studies and provide novel insights into shared psychiatric co-morbidities.

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# Figures and Tables

## Table 1. Characteristics of the patient and control samples by site.

| Center | Age controls (Mean ± SD) | Age cases (Mean ± SD) | Age of onset (Mean ± SD) | Duration of illness (Mean ± SD) | Total controls | Total cases | L TLE-HS cases | R TLE-HS cases | L TLE-NL cases | R TLE-NL cases | GGE cases | ExE cases | Total *n* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Bonn** | 38.0 ± 14.0 | 41.8 ± 12.9 | 17.7 ± 11.6 | 23.8 ± 14.2 | 44 | 64 | 42 | 22 | 0 | 0 | 0 | 0 | 108 |
| **CUBRIC** | 28.3 ± 8.4 | 28.6 ± 7.7 | 14.7 ± 4.0 | 14.0 ± 9.5 | 35 | 34 | 0 | 0 | 0 | 0 | 34 | 0 | 69 |
| **EKUT** | 40.0 ± 14.9 | 33.9 ± 13.1 | 19.3 ± 14.2 | 14.6 ± 10.4 | 19 | 15 | 0 | 0 | 0 | 0 | 15 | 0 | 34 |
| **EPICZ** | 38.6 ± 11.2 | 38.3 ± 9.7 | 19.1 ± 12.4 | 19.2 ± 12.5 | 113 | 86 | 19 | 26 | 26 | 15 | 0 | 0 | 199 |
| **EPIGEN_Ireland** | 34.8 ± 9.5 | 35.9 ± 9.0 | 19.1 ± 10.9 | 18.1 ± 12.9 | 67 | 47 | 9 | 5 | 17 | 16 | 0 | 0 | 114 |
| **Florence** | 34.6 ± 11.6 | 37.6 ± 13.5 | 14.0 ± 7.4 | 19.0 ± 9.9 | 35 | 4 | 0 | 0 | 0 | 2 | 0 | 2 | 39 |
| **Genova** | 25.3 ± 8.2 | 25.3 ± 8.2 | 10.4 ± 4.6 | 14.7 ± 7.7 | 20 | 17 | 0 | 1 | 3 | 4 | 7 | 2 | 37 |
| **Greifswald** | n/a | 34.6 ± 14.0 | 19.2 ± 9.7 | 15.4 ± 9.2 | n/a | 48 | 0 | 0 | 0 | 0 | 35 | 13 | 48 |
| **HFHS_2.6mm** | 29.5 ± 7.0 | 38.3 ± 13.0 | 19.0 ± 16.9 | 19.0 ± 12.9 | 21 | 57 | 6 | 8 | 8 | 7 | 0 | 28 | 78 |
| **HFHS_3mm** | n/a | 40.1 ± 15.4 | - | - | 0 | 14 | 3 | 3 | 3 | 3 | 0 | 2 | 14 |
| **IDIBAPS_31Dir** | n/a | 39.3 ± 10.1 | 22.5 ± 13.4 | 16.4 ± 11.1 | 0 | 25 | 5 | 7 | 3 | 2 | 1 | 7 | 25 |
| **IDIBAPS_39Dir** | 32.4 ± 6.6 | 33.3 ± 9.4 | 16.9 ± 11.8 | 17.6 ± 11.9 | 30 | 19 | 3 | 8 | 0 | 1 | 1 | 6 | 49 |
| **IDIBAPS_88Dir** | 34.1 ± 5.1 | 37.6 ± 10.5 | 15.6 ± 11.0 | 22.0 ± 13.3 | 22 | 27 | 5 | 10 | 3 | 3 | 0 | 6 | 49 |
| **KCL** | 30.4 ± 7.5 | 35.0 ± 9.5 | - | - | 92 | 89 | 24 | 38 | 0 | 0 | 27 | 0 | 181 |
| **Liverpool_Walton** | 31.8 ± 7.7 | 31.1 ± 10.3 | 14.3 ± 8.8 | 16.7 ± 11.9 | 40 | 33 | 5 | 3 | 8 | 5 | 1 | 11 | 73 |
| **Melbourne** | n/a | 37.2 ± 9.9 | 22.4 ± 12.8 | 14.8 ± 11.2 | 0 | 25 | 13 | 5 | 6 | 1 | 0 | 0 | 25 |
| **MNI** | 30.7 ± 7.4 | 32.1 ± 9.5 | 16.4 ± 9.6 | 15.4 ± 10.6 | 46 | 149 | 20 | 22 | 23 | 15 | 0 | 69 | 195 |
| **MUSC** | 55.2 ± 6.6 | 36.6 ± 10.7 | 18.5 ± 13.5 | 17.8 ± 12.1 | 58 | 43 | 19 | 6 | 11 | 7 | 0 | 0 | 101 |
| **NYU** | 30.3 ± 10.0 | 32.6 ± 8.9 | 24.0 ± 12.7 | 8.6 ± 9.9 | 26 | 45 | 2 | 2 | 8 | 3 | 0 | 30 | 71 |
| **UCL** | 37.7 ± 12.4 | 38.7 ± 11.4 | 13.9 ± 10.7 | 24.7 ± 14.3 | 29 | 53 | 24 | 13 | 6 | 10 | 0 | 0 | 82 |
| **UCSD** | 37.3 ± 13.5 | 34.0 ± 11.9 | 19.6 ± 12.9 | 15.2 ± 13.3 | 47 | 55 | 17 | 12 | 13 | 13 | 0 | 0 | 102 |
| **UMG** | 36.0 ± 10.4 | 34.1 ± 10.8 | 16.6 ± 8.1 | 15.6 ± 11.7 | 20 | 36 | 2 | 5 | 0 | 0 | 24 | 5 | 56 |
| **UNAM** | 33.7 ± 12.2 | 31.4 ± 11.7 | 15.8 ± 11.1 | 15.5 ± 12.8 | 34 | 30 | 9 | 10 | 9 | 2 | 0 | 0 | 64 |
| **UNICAMP** | 35.5 ± 10.8 | 40.6 ± 9.9 | 12.3 ± 9.6 | 28.3 ± 12.2 | 271 | 234 | 92 | 74 | 15 | 4 | 37 | 12 | 505 |
| **Combined** | **35.5 ± 11.7** | **36.1 ± 11.2** | **16.3 ± 11.3** | **19.9 ± 13.0** | **1069** | **1249** | **319** | **280** | **162** | **113** | **182** | **193** | **2318** |

**Table 2. Demographic and clinical characteristics of the total sample.** Post-hoc comparisons revealed that controls were younger than both TLE-HS groups and older than patients with GGE and ExE (all p-values<0.05). Both TLE-HS groups and the left TLE-NL group were older than the GGE and ExE groups ($p$<0.05). The right TLE-HS group was older than both TLE-NL groups ($p$<0.05).

| | N | Age (SD) | Sex (% Male) | Age of onset (SD) | Duration of illness (SD) |
|---|---|---|---|---|---|
| **Controls** | 1,069 | 35.5 (11.7) | 41.7 | ----- | ----- |
| **All patients** | 1,249 | 36.1 (11.2) | 42.9 | 16.3 (11.3) | 19.9 (13.0) |
| **Left TLE-HS** | 319 | 38.3 (10.6) | 43.3 | 14.5 (11.5) | 24.2 (13.3) |
| **Right TLE-HS** | 280 | 39.3 (10.8) | 42.5 | 15.3 (11.6) | 24.1 (13.9) |
| **Left TLE-NL** | 162 | 36.1 (10.9) | 38.3 | 18.8 (11.6) | 17.1 (12.1) |
| **Right TLE-NL** | 113 | 35.1 (11.4) | 37.2 | 19.5 (12.2) | 15.1 (11.2) |
| **GGE** | 182 | 31.8 (9.9) | 44.5 | 14.8 (7.3) | 16.8 (10.5) |
| **ExE** | 193 | 32.7 (11.5) | 43.5 | 17.6 (11.1) | 15.1 (11.5) |

**Figure 1. Fiber atlas.**

**Figure 2. dMRI harmonization using ComBat**. Average FA (top) and MD (bottom) measures across 24 scanners showing differences in mean FA measures per scanner (left) which are harmonized using ComBat (middle). The process corrects the variance in scanner without altering the biological variance expected with age (right). Red= *before* correction; Blue= *after* correction.

**Figure 3. FA Effect Size Bar Graphs**

**Figure 4. MD Effect Size Bar Graphs**

**Figure 5. Syndromic difference in average FA and MD in five ROIs.** Mean FA (left) and MD (right) for each patient syndrome, controlling for age, age$^2$, sex, age of onset, and disease duration. Error bars reflect 95% confidence intervals. Dotted red lines reflect the means of controls. For FA, Average=0.585, ACR=0.481, BCC=0.690, CGC=0.627, EC=0.484. For MD, Average=0.000801, ACR=0.000741, BCC=0.000881, CGC=0.000733, EC=0.000739. Significant differences are marked with asterisks (* for $p<0.05$, ** for $p<0.01$, *** for $p<0.001$).

**Figure 6. A). Heat map of FA effect sizes for the "all epilepsies" group compared to those in four other ENIGMA disorders**: SCZ = schizophrenia; BP = bipolar disorder; MDD = major depressive disorder. **B). Radar plot of the four disorders that showed significant correlations across white matter tracts.** Positive values reflect patient group values were on average higher than controls, whereas negative values reflect cases where patient group values were on average lower than that of controls.

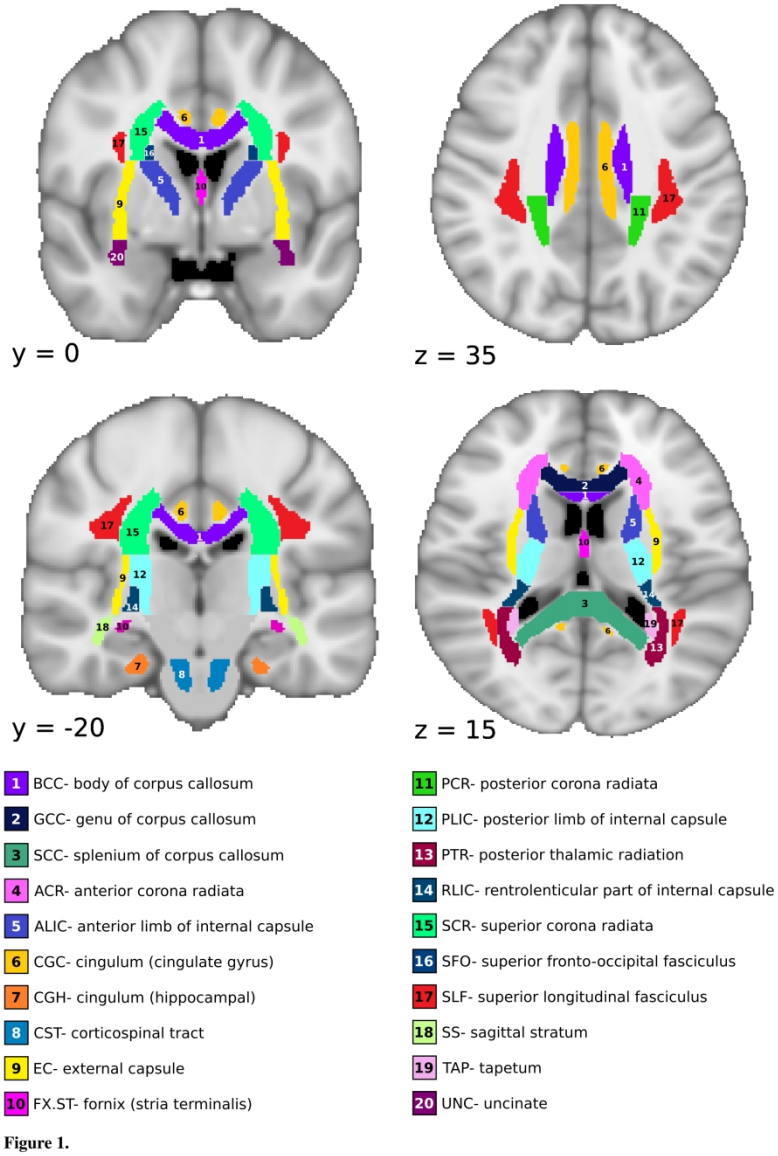


**Figure 1.**

Figure 1. Fiber atlas.

656x926mm (96 x 96 DPI)

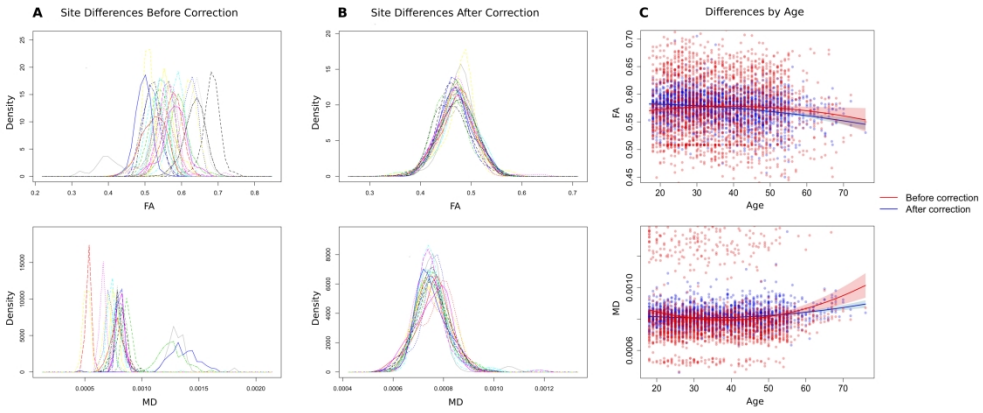


Figure 2.

Figure 2. dMRI harmonization using ComBat. Average FA (top) and MD (bottom) measures across 24 scanners showing differences in mean FA measures per scanner (left) which are harmonized using ComBat (middle). The process corrects the variance in scanner without altering the biological variance expected with age (right). Red= before correction; Blue= after correction.

926x404mm (96 x 96 DPI)

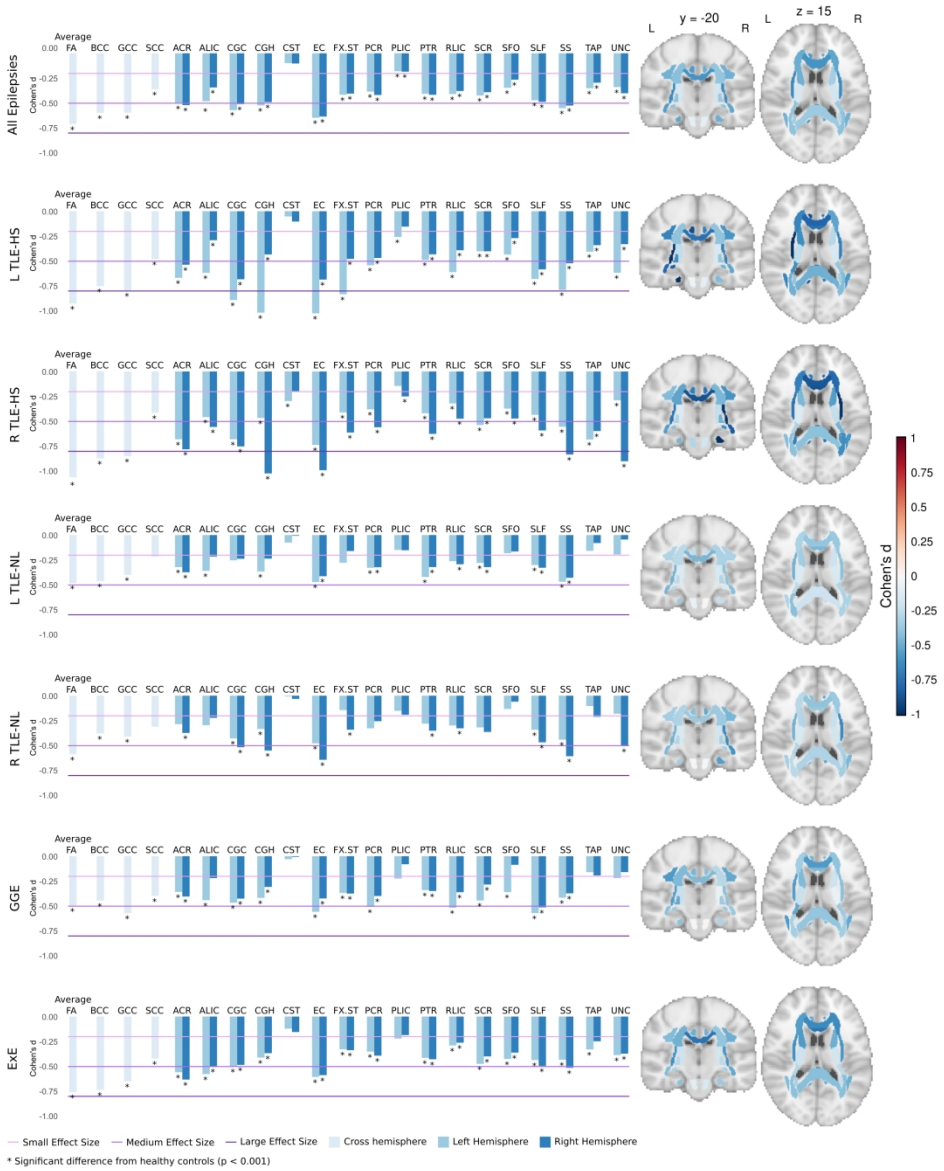


**Figure 3.**

Figure 3. FA Effect Size Bar Graphs

656x825mm (96 x 96 DPI)

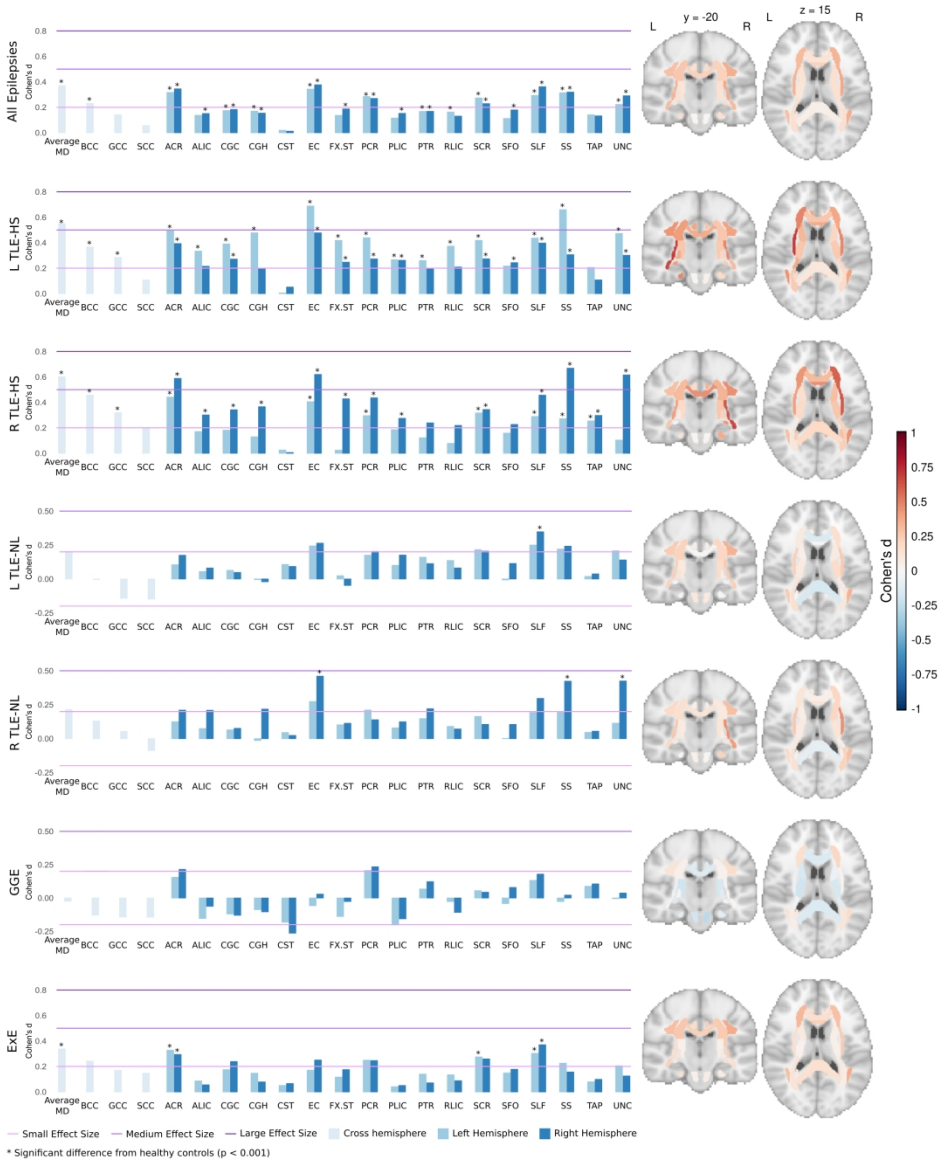


**Figure 4.**

Figure 4. MD Effect Size Bar Graphs

656x825mm (96 x 96 DPI)

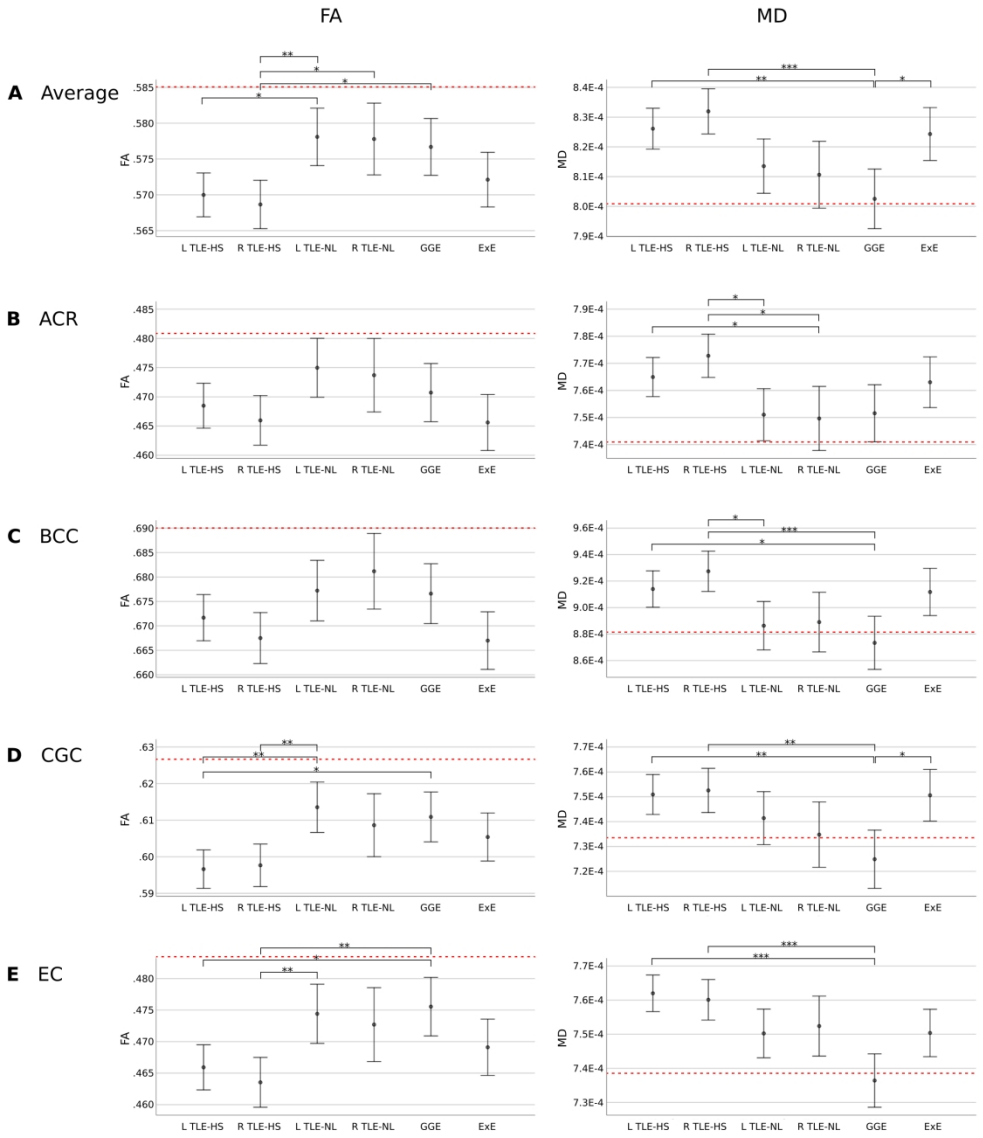


**Figure 5.**

Figure 5. Syndromic difference in average FA and MD in five ROIs. Mean FA (left) and MD (right) for each patient syndrome, controlling for age, age2, sex, age of onset, and disease duration. Error bars reflect 95% confidence intervals. Dotted red lines reflect the means of controls. For FA, Average=0.585, ACR=0.481, BCC=0.690, CGC=0.627, EC=0.484. For MD, Average=0.000801, ACR=0.000741, BCC=0.000881, CGC=0.000733, EC=0.000739. Significant differences are marked with asterisks (* for $p<0.05$, ** for $p<0.01$, *** for $p<0.001$).

656x772mm (96 x 96 DPI)

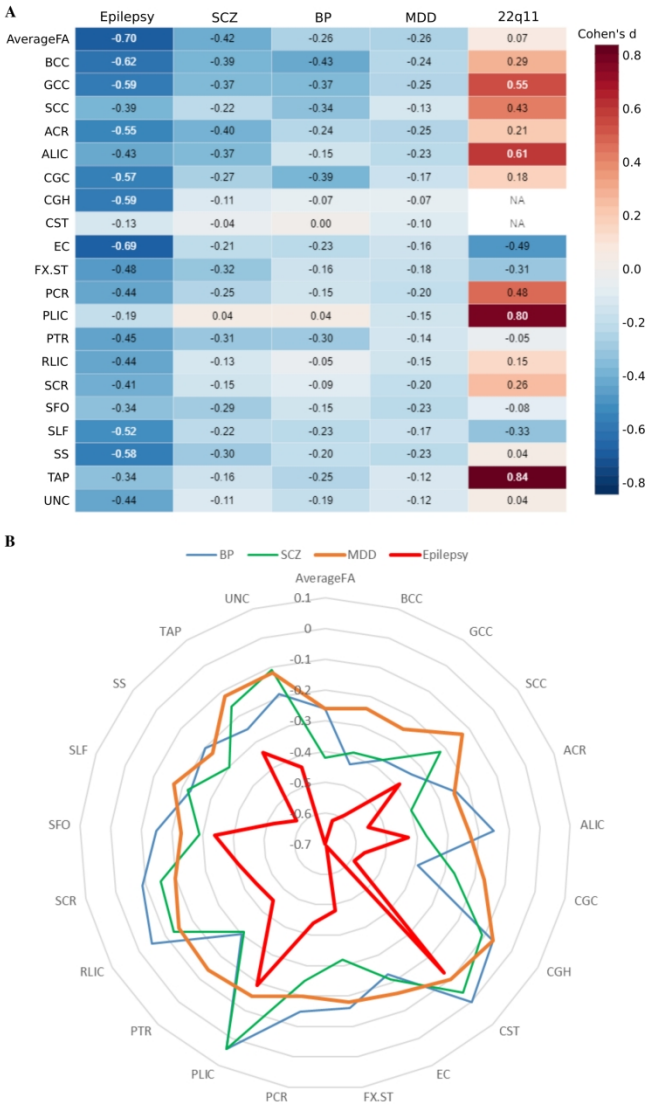


**Figure 6.**

Figure 6. A). Heat map of FA effect sizes for the "all epilepsies" group compared to those in four other ENIGMA disorders: SCZ = schizophrenia; BP = bipolar disorder; MDD = major depressive disorder. B). Radar plot of the four disorders that showed significant correlations across white matter tracts. Positive values reflect patient group values were on average higher than controls, whereas negative values reflect cases where patient group values were on average lower than that of controls.

476x820mm (96 x 96 DPI)

Supplementary Information

**Supplementary Table 1.** Scanner protocols by each research center.

**Supplementary Table 2.** Descriptive statistics before and after ComBat harmonization.

**Supplementary Table 3.** Multivariate tests.

**Supplementary Figure 1.** RD effect size graphs.

**Supplementary Figure 2.** AD effect size graphs.

**Supplementary Table 4.** Effect sizes for FA differences between healthy controls and each syndrome.

**Supplementary Table 5.** Effect sizes for MD differences between healthy controls and each syndrome.

**Supplementary Table 6.** Effect sizes for RD differences between healthy controls and each syndrome.

**Supplementary Table 7.** Effect sizes for AD differences between healthy controls and each syndrome.

**Supplementary Table 8.** Relationship between FA and age of disease onset by syndrome.

**Supplementary Table 9.** Relationship between FA and disease duration by syndrome.

**Supplementary Table 10.** Relationship between MD and age of disease onset by syndrome.

**Supplementary Table 11.** Relationship between MD and disease duration by syndrome.

**Supplementary Table 12.** Relationship between RD and age of disease onset by syndrome.

**Supplementary Table 13.** Relationship between RD and disease duration by syndrome.

**Supplementary Table 14.** Relationship between AD and age of disease onset by syndrome.

**Supplementary Table 15.** Relationship between AD and disease duration by syndrome.

**Supplementary Table 16.** Follow-up permutation testing of FA differences between controls and epilepsy patients.

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**Supplementary Table 1.** Scanner protocols by each research center. An asterisk (*) indicates a variable TR due to cardiac gating.

| Center | Scanner | Orientation | # of Slices | Voxel Size (mm3) | Gradient Directions | b-value (mm/s2) | # b=0 scans | TE (ms) | TR (ms) | Relevant Citation |
|---|---|---|---|---|---|---|---|---|---|---|
| **Bonn** | Siemens Trio | Axial | 160 | 1 x 1 x 1 | 60 | 1000 | 7 | 3.97 | 1300 | Kreilkamp, B. A., Weber, B., Richardson, M. P., & Keller, S. S. (2017). Automated tractography in patients with temporal lobe epilepsy using TRActs Constrained by UnderLying Anatomy (TRACULA). *NeuroImage: Clinical,14*, 67-76. doi:10.1016/j.nicl.2017.01.003 |
| **CUBRIC** | GE Signa HDx | - | 60 | 2.4 mm slice thickness | 30 | 1200 | 3 | 87 | * | Caeyenberghs, K., Powell, H., Thomas, R., Brindley, L., Church, C., Evans, J., . . . Hamandi, K. (2015). Hyperconnectivity in juvenile myoclonic epilepsy: A network analysis. *NeuroImage: Clinical,7*, 98-104. doi:10.1016/j.nicl.2014.11.018 |
| **EKUT** | Siemens Trio | - | 52 | 1.81 x 1.81 x 1.79 | 48 | 1200 (2x) | 6 (2x) | 93 | 9400 | - |
| **EPICZ** | GE Discovery MR750 | Axial | 80 | 2 x 2 x 2 | 27 | 1000 | 4 | 81.4 | 10000 | Caligiuri, M. E., Labate, A., Cherubini, A., Mumoli, L., Ferlazzo, E., Aguglia, U., . . . Gambardella, A. (2016). Integrity of the corpus callosum in patients with benign temporal lobe epilepsy. *Epilepsia,57*(4), 590-596. doi:10.1111/epi.13339 |
| **EPIGEN-Ireland** | Philips Achieva | Axial | 70 | 1.75 x 1.75 x 2 | 32 | 1000 | - | 52 | 12786 | Whelan, C. D., Alhusaini, S., Ohanlon, E., Cheung, M., Iyer, P. M., Meaney, J. F., . . . Cavalleri, G. L. (2015). White matter alterations in patients with MRI-negative temporal lobe epilepsy and their asymptomatic siblings. *Epilepsia,56*(10), 1551-1561. doi:10.1111/epi.13103 |
| **Florence** | Philips Achieva | - | 69 | 2 x 2 x 2 | 32 | 1000 | 1 | 80 | 4000 | - |
| **Genova** | Philips Ingenia | Axial | 65 | 2 x 2 x 2 | 64 | 1000 | 1 | 90 | 7000 | - |
| **Greifswald** | Siemens Verio | - | 80 | 1.8 x 1.8 x 1.8 | 64 | 1000 | 1 | 107 | 15300 | Domin, M., Bartels, S., Geithner, J., Wang, Z. I., Runge, U., Grothe, M., . . . Podewils, F. V. (2018). Juvenile Myoclonic Epilepsy Shows Potential Structural White Matter Abnormalities: A TBSS Study. *Frontiers in* |

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|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | *Neurology,9*. doi:10.3389/fneur.2018.00509 |
| **Henry Ford** | GE Signa | Axial | 60 | 1.96 × 1.96 × 2.6 | 25 | 1000 | 1 | 76 | 7500 | Nazem-Zadeh, M., Bowyer, S. M., Moran, J. E., Davoodi-Bojd, E., Zillgitt, A., Weiland, B. J., . . . Soltanian-Zadeh, H. (2016). MEG Coherence and DTI Connectivity in mTLE. *Brain Topography,29*(4), 598-622. doi:10.1007/s10548-016-0488-0 |
| **IDIBAPS_31DIR** | Siemens Trio | Axial | 55 | 2.4 x 2.4 x 2.4 | 30 | 1000 | 1 | 90 | 6900 | |
| **IDIBAPS_39DIR** | Siemens Trio | Axial | 64 | 1.97 x 1.97 x 2 | 36 | 1000 | 3 | 88 | 8138 | Córdova-Palomera, A., Reus, M. A., Fatjó-Vilas, M., Falcón, C., Bargalló, N., Heuvel, M. P., & Fañanás, L. (2016). FKBP5 modulates the hippocampal connectivity deficits in depression: A study in twins. *Brain Imaging and Behavior,11*(1), 62-75. doi:10.1007/s11682-015-9503-4 |
| **IDIBAPS_88DIR** | Siemens Trio | Axial | 55 | 1.25 x 1.25 x 2.5 | 82 | 1000 | 6 | 98 | 7600 | Aparicio, J., Carreño, M., Bargalló, N., Setoain, X., Rubí, S., Rumià, J., . . . Donaire, A. (2016). Combined 18 F-FDG-PET and diffusion tensor imaging in mesial temporal lobe epilepsy with hippocampal sclerosis. *NeuroImage: Clinical,12*, 976-989. doi:10.1016/j.nicl.2016.05.002 |
| **KCL** | GE Discovery MR750 | Axial | 66 | 2.4 x 2.4 x 2.4 | 32 | 1000 | 6 | 75 | * | - |
| **Liverpool_Walton** | GE Discovery MR750 | Axial | 66 | 1 x 1 x 2 | 60 | 1000 | 6 | 82 | 8000 | Kreilkamp, B. A., Weber, B., Richardson, M. P., & Keller, S. S. (2017). Automated tractography in patients with temporal lobe epilepsy using TRActs Constrained by UnderLying Anatomy (TRACULA). *NeuroImage: Clinical,14*, 67-76. doi:10.1016/j.nicl.2017.01.003 |
| **MNI** | Siemens Trio | Axial | 63 | 2 x 2 x 2 | 64 | 1000 | 1 | 90 | 8400 | Liu, M., Bernhardt, B. C., Hong, S., Caldairou, B., Bernasconi, A., & Bernasconi, N. (2016). The superficial white matter in temporal lobe epilepsy: A key link between structural and functional network disruptions. *Brain,139*(9), 2431-2440. doi:10.1093/brain/aww167 |
| **NYU** | Siemens Allegra | Axial | 60 | 2.5 x 2.5 x 2.5 | 64 | 3000 | 8 | 99 | 7900 | - |

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| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Melbourne** | Siemens Trio | Axial | 55 | 2.5 x 2.5 x 2.5 | 64 | 3000 | 1 | 122 | 8700 | - |
| **UCL** | GE Signa HDx | Axial | 60 | 1.875×1.875×2.4 | 52 | 1200 | 6 | 73 | * | Taylor, P. N., Sinha, N., Wang, Y., Vos, S. B., Tisi, J. D., Miserocchi, A., . . . Duncan, J. S. (2018). The impact of epilepsy surgery on the structural connectome and its relation to outcome. *NeuroImage: Clinical,18*, 202-214. doi:10.1016/j.nicl.2018.01.028 |
| **UCSD** | GE Discovery MR750 | Axial | 53 | 1.86 x 1.86 x 2.5 | 30 | 1000 | 2 | 82.9 | 8000 | Reyes, A., Paul, B. M., Marshall, A., Chang, Y. A., Bahrami, N., Kansal, L., . . . Mcdonald, C. R. (2018). Does bilingualism increase brain or cognitive reserve in patients with temporal lobe epilepsy? *Epilepsia,59*(5), 1037-1047. doi:10.1111/epi.14072 |
| **UMG** | Siemens Trio | - | 31 | 1.89 x 1.89 x 1.89 | 30 | 1000 | 1 | 93 | 10000 | Bonilha, L., Gleichgerrcht, E., Fridriksson, J., Rorden, C., Breedlove, J. L., Nesland, T., . . . Focke, N. K. (2015). Reproducibility of the Structural Brain Connectome Derived from Diffusion Tensor Imaging. *Plos One,10*(9). doi:10.1371/journal.pone.0135247 |
| **UNAM** | Philips Achieva | - | - | 2 x 2 x 2 | 60 | 2000 | 1 | 64.3 | 11860 | Rodríguez-Cruces, R., Velázquez-Pérez, L., Rodríguez-Leyva, I., Velasco, A. L., Trejo-Martínez, D., Barragán-Campos, H. M., . . . Concha, L. (2018). Association of white matter diffusion characteristics and cognitive deficits in temporal lobe epilepsy. *Epilepsy & Behavior,79*, 138-145. doi:10.1016/j.yebeh.2017.11.040 |
| **UNICAMP** | Philips Achieva | Axial | 70 | 2 x 2 x 2 | 32 | 1000 | 1 | 61 | 8500 | Campos, B. M., Coan, A. C., Beltramini, G. C., Liu, M., Yassuda, C. L., Ghizoni, E., . . . Cendes, F. (2014). White matter abnormalities associate with type and localization of focal epileptogenic lesions. *Epilepsia,56*(1), 125-132. doi:10.1111/epi.12871 |

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**Supplementary Table 2.** Descriptive statistics before and after ComBat harmonization.

| | | | *Before harmonization* | | *After harmonization* | |
|---|---|---|---|---|---|---|
| **Diffusivity measure** | **Diagnostic group** | **n** | **Mean** | **SD** | **Mean** | **SD** |
| **FA** | Controls | 1069 | 0.586 | 0.053 | 0.585 | 0.021 |
| | GGE | 182 | 0.596 | 0.069 | 0.575 | 0.022 |
| | TLE-HS-Left | 319 | 0.561 | 0.051 | 0.565 | 0.027 |
| | TLE-HS-Right | 280 | 0.556 | 0.055 | 0.560 | 0.031 |
| | TLE-NL-Left | 162 | 0.569 | 0.043 | 0.574 | 0.026 |
| | TLE-NL-Right | 113 | 0.566 | 0.041 | 0.575 | 0.027 |
| | ExE | 193 | 0.566 | 0.053 | 0.569 | 0.027 |
| **MD** | Controls | 977 | 8.02E-04 | 1.88E-04 | 8.03E-04 | 5.45E-05 |
| | GGE | 120 | 7.98E-04 | 1.50E-04 | 8.06E-04 | 5.99E-05 |
| | TLE-HS-Left | 295 | 8.39E-04 | 2.19E-04 | 8.33E-04 | 6.34E-05 |
| | TLE-HS-Right | 242 | 8.31E-04 | 1.89E-04 | 8.39E-04 | 6.41E-05 |
| | TLE-NL-Left | 162 | 8.30E-04 | 2.20E-04 | 8.11E-04 | 5.80E-05 |
| | TLE-NL-Right | 113 | 9.13E-04 | 2.48E-04 | 8.16E-04 | 6.29E-05 |
| | ExE | 180 | 7.58E-04 | 1.24E-04 | 8.21E-04 | 5.95E-05 |
| **AD** | Controls | 975 | 1.33E-03 | 1.62E-04 | 1.33E-03 | 1.03E-04 |
| | GGE | 120 | 1.30E-03 | 6.24E-05 | 1.31E-03 | 1.06E-04 |
| | TLE-HS-Left | 295 | 1.34E-03 | 2.03E-04 | 1.34E-03 | 1.08E-04 |
| | TLE-HS-Right | 242 | 1.34E-03 | 1.66E-04 | 1.34E-03 | 9.81E-05 |
| | TLE-NL-Left | 162 | 1.33E-03 | 2.29E-04 | 1.32E-03 | 9.14E-05 |
| | TLE-NL-Right | 113 | 1.44E-03 | 5.13E-04 | 1.33E-03 | 1.54E-04 |
| | ExE | 180 | 1.26E-03 | 1.96E-04 | 1.32E-03 | 9.40E-05 |
| **RD** | Controls | 977 | 5.53E-04 | 2.52E-04 | 5.59E-04 | 5.58E-05 |
| | GGE | 120 | 5.47E-04 | 2.11E-04 | 5.69E-04 | 6.20E-05 |
| | TLE-HS-Left | 295 | 6.18E-04 | 3.04E-04 | 5.98E-04 | 6.76E-05 |
| | TLE-HS-Right | 242 | 5.97E-04 | 2.63E-04 | 6.05E-04 | 7.04E-05 |
| | TLE-NL-Left | 162 | 5.97E-04 | 2.74E-04 | 5.70E-04 | 6.06E-05 |
| | TLE-NL-Right | 113 | 7.03E-04 | 3.46E-04 | 5.75E-04 | 6.24E-05 |
| | ExE | 180 | 5.05E-04 | 1.16E-04 | 5.83E-04 | 6.45E-05 |

**Supplementary Table 3. Multivariate tests.** Increasing values of Pillai's trace indicate effects that contribute more to the model.

| Measure | Effect | Pillai's Trace | F | Hypothesis df | Error df | Sig. | Partial $\eta^2$ | Observed Power |
|---|---|---|---|---|---|---|---|---|
| FA | Diagnosis | 0.44 | 4.70 | 228 | 13452 | <0.001 | 0.074 | 1.0 |
| | Age | 0.05 | 2.90 | 38 | 2237 | <0.001 | 0.047 | 1.0 |
| | $Age^2$ | 0.04 | 2.33 | 38 | 2237 | <0.001 | 0.038 | 1.0 |
| | Sex | 0.14 | 9.27 | 38 | 2237 | <0.001 | 0.136 | 1.0 |
| | Sex*Diagnosis | 0.13 | 1.33 | 228 | 13416 | 0.001 | 0.022 | 1.0 |
| MD | Diagnosis | 0.31 | 2.80 | 228 | 11688 | <0.001 | 0.052 | 1.0 |
| | Age | 0.07 | 3.67 | 38 | 1943 | <0.001 | 0.067 | 1.0 |
| | $Age^2$ | 0.05 | 2.94 | 38 | 1943 | <0.001 | 0.054 | 1.0 |
| | Sex | 0.12 | 6.77 | 38 | 1943 | <0.001 | 0.117 | 1.0 |
| | Sex*Diagnosis | 0.13 | 1.08 | 228 | 11652 | 0.870 | 0.021 | 1.0 |
| AD | Diagnosis | 0.22 | 1.96 | 228 | 11946 | <0.001 | 0.036 | 1.0 |
| | Age | 0.07 | 4.05 | 38 | 1986 | <0.001 | 0.072 | 1.0 |
| | $Age^2$ | 0.05 | 2.98 | 38 | 1986 | <0.001 | 0.054 | 1.0 |
| | Sex | 0.10 | 5.77 | 38 | 1986 | <0.001 | 0.099 | 1.0 |
| | Sex*Diagnosis | 0.12 | 1.07 | 228 | 11910 | 0.215 | 0.020 | 1.0 |
| RD | Diagnosis | 0.36 | 3.28 | 228 | 11790 | <0.001 | 0.060 | 1.0 |
| | Age | 0.07 | 4.16 | 38 | 1960 | <.001 | 0.075 | 1.0 |
| | $Age^2$ | 0.06 | 3.58 | 38 | 1960 | <.001 | 0.065 | 1.0 |
| | Sex | 0.11 | 6.65 | 38 | 1960 | <.001 | 0.114 | 1.0 |
| | Sex*Diagnosis | 0.13 | 1.18 | 228 | 11754 | 0.033 | 0.022 | 1.0 |

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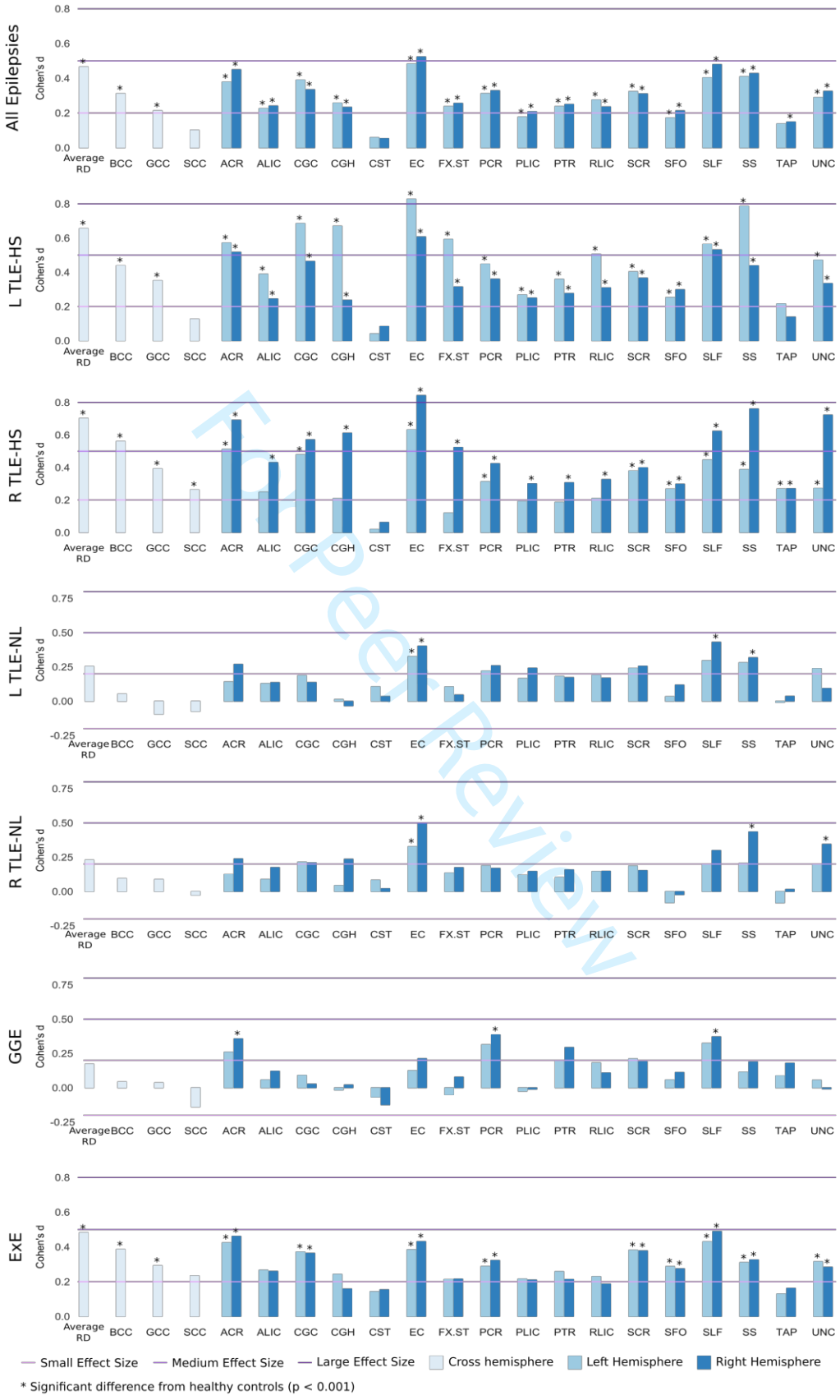


**Supplementary Figure 1.** RD effect size graphs.

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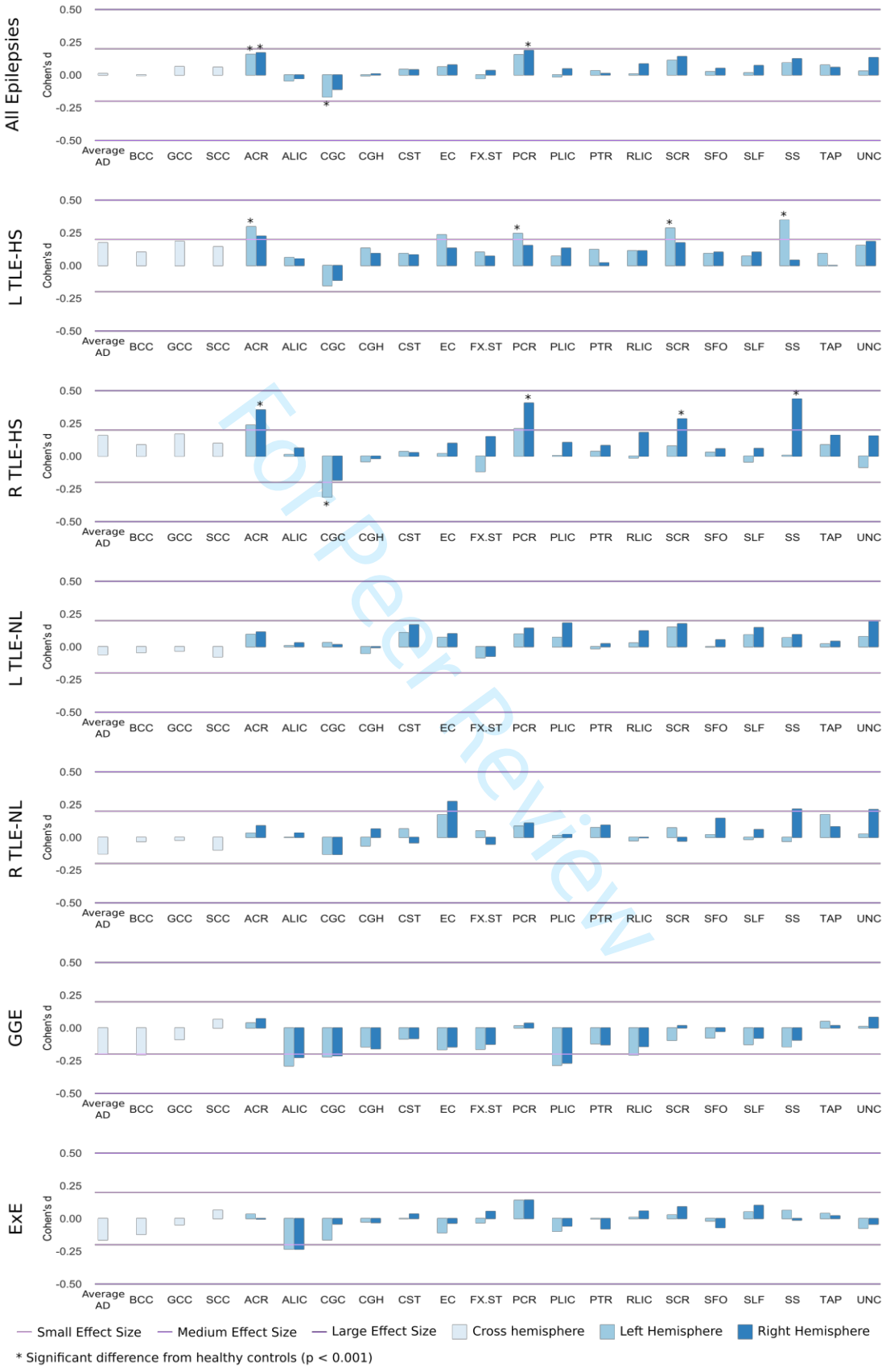


**Supplementary Figure 2.** AD effect size graphs.

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**Supplementary Table 4.** Effect sizes for FA differences between healthy controls and each syndrome.

| | All Epilepsies | | L TLE-HS | | R TLE-HS | | L TLE-NL | | R TLE-NL | | GGE | | ExE | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **ROI** | Cohen's d | P value | Cohen's d | P value | Cohen's d | P value | Cohen's d | P value | Cohen's d | P value | Cohen's d | P value | Cohen's d | P value |
| **AverageFA** | -0.71 | 2.3E-59 | -0.92 | 6.6E-40 | -1.06 | 5.4E-46 | -0.48 | 1.8E-07 | -0.58 | 4.8E-08 | -0.49 | 4.5E-10 | -0.75 | 1.1E-19 |
| **BCC** | -0.59 | 1.3E-45 | -0.75 | 1.0E-26 | -0.87 | 2.9E-34 | -0.46 | 1.1E-07 | -0.37 | 1.1E-04 | -0.44 | 1.8E-08 | -0.73 | 9.4E-20 |
| **GCC** | -0.59 | 1.5E-43 | -0.79 | 2.6E-28 | -0.85 | 2.4E-33 | -0.39 | 9.8E-06 | -0.40 | 9.9E-05 | -0.57 | 1.1E-11 | -0.64 | 9.5E-16 |
| **SCC** | -0.36 | 4.9E-17 | -0.48 | 1.7E-10 | -0.41 | 6.6E-10 | -0.21 | 2.9E-02 | -0.31 | 0.005 | -0.39 | 1.1E-06 | -0.42 | 4.2E-07 |
| **ACR.L** | -0.50 | 3.0E-32 | -0.66 | 1.1E-21 | -0.68 | 3.4E-22 | -0.32 | 2.0E-04 | -0.28 | 0.006 | -0.35 | 3.9E-06 | -0.55 | 9.8E-13 |
| **ACR.R** | -0.52 | 1.2E-33 | -0.53 | 3.7E-14 | -0.78 | 2.0E-27 | -0.37 | 6.1E-05 | -0.37 | 4.0E-04 | -0.40 | 6.3E-07 | -0.63 | 2.8E-14 |
| **ALIC.L** | -0.48 | 7.0E-26 | -0.61 | 5.6E-20 | -0.45 | 1.1E-09 | -0.35 | 4.4E-05 | -0.29 | 0.002 | -0.44 | 5.7E-07 | -0.57 | 8.6E-12 |
| **ALIC.R** | -0.34 | 1.8E-15 | -0.28 | 9.8E-06 | -0.55 | 2.8E-15 | -0.21 | 0.016 | -0.22 | 0.024 | -0.21 | 0.006 | -0.49 | 2.1E-09 |
| **CGC.L** | -0.57 | 2.7E-38 | -0.89 | 1.6E-36 | -0.68 | 3.2E-21 | -0.25 | 0.004 | -0.42 | 2.4E-05 | -0.46 | 4.6E-08 | -0.49 | 8.2E-10 |
| **CGC.R** | -0.50 | 8.3E-34 | -0.68 | 2.6E-24 | -0.75 | 1.2E-25 | -0.23 | 0.008 | -0.51 | 5.9E-07 | -0.42 | 3.8E-07 | -0.48 | 4.1E-09 |
| **CGH.L** | -0.52 | 3.3E-35 | -1.01 | 1.4E-50 | -0.46 | 9.6E-11 | -0.36 | 1.5E-05 | -0.33 | 7.1E-04 | -0.41 | 2.5E-07 | -0.41 | 3.7E-07 |
| **CGH.R** | -0.48 | 6.0E-30 | -0.43 | 6.0E-11 | -1.02 | 8.4E-46 | -0.23 | 0.012 | -0.55 | 5.2E-08 | -0.30 | 2.1E-04 | -0.36 | 6.6E-06 |
| **CST.L** | -0.09 | 0.009 | -0.05 | 0.319 | -0.29 | 9.0E-05 | -0.07 | 0.378 | 0.00 | 0.921 | -0.02 | 0.729 | -0.11 | 0.140 |
| **CST.R** | -0.10 | 0.021 | -0.10 | 0.099 | -0.19 | 0.002 | 0.00 | 0.910 | -0.02 | 0.722 | 0.00 | 0.935 | -0.15 | 0.072 |
| **EC.L** | -0.64 | 5.3E-53 | -1.02 | 4.6E-49 | -0.73 | 1.8E-25 | -0.47 | 1.1E-07 | -0.47 | 2.1E-06 | -0.55 | 3.7E-12 | -0.60 | 5.4E-14 |
| **EC.R** | -0.63 | 2.7E-47 | -0.68 | 4.7E-25 | -0.99 | 2.3E-42 | -0.41 | 1.5E-06 | -0.64 | 2.6E-10 | -0.42 | 7.7E-07 | -0.58 | 2.0E-13 |
| **FX.ST.L** | -0.41 | 1.6E-23 | -0.83 | 4.8E-33 | -0.41 | 4.0E-09 | -0.27 | 0.002 | -0.14 | 0.175 | -0.36 | 7.3E-06 | -0.32 | 3.1E-05 |
| **FX.ST.R** | -0.40 | 8.5E-21 | -0.47 | 1.1E-12 | -0.61 | 1.7E-18 | -0.15 | 0.050 | -0.34 | 9.3E-04 | -0.37 | 7.5E-06 | -0.33 | 4.4E-05 |
| **PCR.L** | -0.38 | 1.9E-21 | -0.54 | 1.9E-14 | -0.37 | 2.2E-08 | -0.32 | 4.3E-04 | -0.32 | 0.003 | -0.50 | 4.1E-10 | -0.35 | 1.5E-05 |
| **PCR.R** | -0.41 | 4.9E-23 | -0.46 | 1.1E-11 | -0.55 | 1.3E-15 | -0.32 | 1.3E-04 | -0.25 | 0.012 | -0.39 | 3.8E-07 | -0.39 | 2.6E-07 |
| **PLIC.L** | -0.17 | 7.0E-06 | -0.25 | 9.9E-05 | -0.14 | 0.066 | -0.14 | 0.119 | -0.15 | 0.122 | -0.22 | 0.003 | -0.21 | 0.009 |
| **PLIC.R** | -0.18 | 1.4E-05 | -0.15 | 0.009 | -0.24 | 2.1E-04 | -0.15 | 0.079 | -0.18 | 0.065 | -0.07 | 0.195 | -0.18 | 0.009 |
| **PTR.L** | -0.40 | 5.3E-20 | -0.48 | 2.4E-11 | -0.41 | 6.5E-10 | -0.42 | 3.9E-06 | -0.27 | 0.006 | -0.33 | 1.7E-05 | -0.41 | 3.8E-07 |
| **PTR.R** | -0.41 | 2.0E-21 | -0.43 | 6.8E-09 | -0.62 | 1.2E-18 | -0.32 | 2.9E-04 | -0.35 | 5.5E-04 | -0.34 | 8.0E-05 | -0.42 | 4.1E-07 |
| **RLIC.L** | -0.40 | 1.4E-20 | -0.61 | 2.1E-18 | -0.31 | 1.9E-06 | -0.26 | 0.002 | -0.29 | 0.006 | -0.51 | 2.3E-10 | -0.28 | 1.6E-04 |
| **RLIC.R** | -0.37 | 1.8E-17 | -0.39 | 3.0E-09 | -0.47 | 2.9E-11 | -0.29 | 6.1E-04 | -0.32 | 9.5E-04 | -0.36 | 5.8E-06 | -0.26 | 7.3E-04 |
| **SCR.L** | -0.42 | 3.0E-22 | -0.40 | 4.4E-09 | -0.53 | 3.2E-13 | -0.27 | 8.1E-04 | -0.31 | 0.002 | -0.44 | 1.4E-08 | -0.47 | 4.2E-09 |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **SCR.R** | -0.39 | 3.1E-18 | -0.40 | 1.3E-08 | -0.46 | 4.8E-12 | -0.32 | 7.9E-04 | -0.36 | 0.001 | -0.28 | 3.2E-04 | -0.39 | 2.6E-07 |
| **SFO.L** | -0.34 | 1.1E-15 | -0.43 | 4.1E-11 | -0.37 | 6.3E-08 | -0.18 | 4.5E-02 | -0.13 | 0.169 | -0.35 | 1.8E-05 | -0.42 | 4.5E-08 |
| **SFO.R** | -0.26 | 1.6E-09 | -0.26 | 4.3E-05 | -0.47 | 5.0E-11 | -0.16 | 7.7E-02 | -0.05 | 0.702 | -0.08 | 0.332 | -0.36 | 9.6E-06 |
| **SLF.L** | -0.47 | 1.5E-28 | -0.67 | 2.3E-23 | -0.43 | 2.6E-09 | -0.30 | 4.6E-04 | -0.34 | 4.5E-04 | -0.57 | 5.0E-12 | -0.43 | 6.5E-08 |
| **SLF.R** | -0.48 | 2.0E-32 | -0.58 | 7.7E-18 | -0.59 | 2.3E-17 | -0.32 | 1.5E-04 | -0.46 | 3.4E-06 | -0.51 | 4.8E-11 | -0.49 | 4.1E-10 |
| **SS.L** | -0.55 | 6.4E-36 | -0.78 | 1.2E-29 | -0.55 | 1.4E-16 | -0.46 | 1.0E-07 | -0.44 | 2.2E-05 | -0.41 | 9.9E-07 | -0.43 | 1.4E-07 |
| **SS.R** | -0.52 | 6.3E-35 | -0.52 | 4.3E-14 | -0.83 | 2.0E-31 | -0.42 | 1.1E-06 | -0.60 | 9.7E-09 | -0.37 | 2.1E-05 | -0.51 | 5.8E-10 |
| **TAP.L** | -0.35 | 2.8E-15 | -0.40 | 2.1E-09 | -0.68 | 6.7E-22 | -0.15 | 0.091 | -0.10 | 0.398 | -0.15 | 0.057 | -0.32 | 9.8E-05 |
| **TAP.R** | -0.29 | 1.4E-12 | -0.33 | 2.0E-06 | -0.59 | 9.1E-18 | -0.07 | 0.308 | -0.21 | 0.035 | -0.19 | 0.033 | -0.24 | 0.002 |
| **UNC.L** | -0.33 | 4.1E-16 | -0.61 | 1.9E-19 | -0.28 | 3.2E-05 | -0.19 | 0.019 | -0.17 | 0.071 | -0.21 | 0.008 | -0.38 | 1.6E-06 |
| **UNC.R** | -0.40 | 2.1E-20 | -0.32 | 8.3E-07 | -0.90 | 9.3E-37 | -0.04 | 0.698 | -0.50 | 8.5E-07 | -0.15 | 0.067 | -0.37 | 3.6E-06 |

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**Supplementary Table 5.** Effect sizes for MD differences between healthy controls and each syndrome.

| | All Epilepsies | | L TLE-HS | | R TLE-HS | | L TLE-NL | | R TLE-NL | | GGE | | ExE | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **ROI** | Cohen's d | P value | Cohen's d | P value | Cohen's d | P value | Cohen's d | P value | Cohen's d | P value | Cohen's d | P value | Cohen's d | P value |
| **AverageMD** | 0.37 | 3.3E-16 | 0.55 | 3.4E-15 | 0.60 | 3.8E-15 | 0.20 | 0.020 | 0.21 | 0.039 | -0.02 | 0.813 | 0.34 | 4.9E-05 |
| **BCC** | 0.23 | 3.2E-07 | 0.37 | 1.2E-07 | 0.46 | 1.9E-09 | 0.00 | 1.000 | 0.13 | 0.212 | -0.13 | 0.200 | 0.24 | 0.004 |
| **GCC** | 0.14 | 0.002 | 0.28 | 4.0E-05 | 0.32 | 2.7E-05 | -0.14 | 0.101 | 0.05 | 0.604 | -0.14 | 0.157 | 0.17 | 0.041 |
| **SCC** | 0.06 | 0.210 | 0.11 | 0.123 | 0.20 | 0.007 | -0.15 | 0.088 | -0.09 | 0.398 | -0.14 | 0.154 | 0.15 | 0.079 |
| **ACR.L** | 0.32 | 2.5E-12 | 0.49 | 1.3E-12 | 0.44 | 6.7E-09 | 0.10 | 0.227 | 0.12 | 0.228 | 0.16 | 0.121 | 0.33 | 8.4E-05 |
| **ACR.R** | 0.34 | 2.7E-14 | 0.39 | 1.4E-08 | 0.59 | 1.5E-14 | 0.17 | 0.044 | 0.21 | 0.042 | 0.21 | 0.033 | 0.29 | 4.0E-04 |
| **ALIC.L** | 0.14 | 0.002 | 0.33 | 1.4E-06 | 0.17 | 0.024 | 0.05 | 0.530 | 0.07 | 0.472 | -0.15 | 0.127 | 0.09 | 0.299 |
| **ALIC.R** | 0.15 | 8.1E-04 | 0.21 | 0.002 | 0.30 | 7.5E-05 | 0.08 | 0.351 | 0.21 | 0.044 | -0.06 | 0.535 | 0.06 | 0.504 |
| **CGC.L** | 0.17 | 1.1E-04 | 0.39 | 2.0E-08 | 0.18 | 0.017 | 0.06 | 0.463 | 0.06 | 0.533 | -0.12 | 0.233 | 0.18 | 0.035 |
| **CGC.R** | 0.18 | 4.6E-05 | 0.27 | 8.7E-05 | 0.34 | 6.6E-06 | 0.05 | 0.578 | 0.08 | 0.464 | -0.13 | 0.197 | 0.24 | 0.004 |
| **CGH.L** | 0.17 | 1.7E-04 | 0.48 | 6.1E-12 | 0.13 | 0.087 | 0.00 | 0.958 | -0.01 | 0.896 | -0.09 | 0.384 | 0.15 | 0.078 |
| **CGH.R** | 0.15 | 6.4E-04 | 0.20 | 0.004 | 0.37 | 1.4E-06 | -0.02 | 0.816 | 0.22 | 0.036 | -0.10 | 0.302 | 0.08 | 0.345 |
| **CST.L** | 0.02 | 0.670 | 0.01 | 0.936 | 0.03 | 0.737 | 0.11 | 0.220 | 0.05 | 0.663 | -0.18 | 0.070 | 0.05 | 0.540 |
| **CST.R** | 0.01 | 0.780 | 0.05 | 0.454 | 0.01 | 0.937 | 0.09 | 0.287 | 0.02 | 0.819 | -0.26 | 0.009 | 0.07 | 0.427 |
| **EC.L** | 0.34 | 4.2E-14 | 0.69 | 1.3E-22 | 0.41 | 9.0E-08 | 0.24 | 0.005 | 0.27 | 0.008 | -0.06 | 0.566 | 0.17 | 0.040 |
| **EC.R** | 0.38 | 1.1E-16 | 0.48 | 6.3E-12 | 0.62 | 6.3E-16 | 0.26 | 0.002 | 0.46 | 1.0E-05 | 0.03 | 0.772 | 0.25 | 0.003 |
| **FX.ST.L** | 0.14 | 0.002 | 0.42 | 1.8E-09 | 0.02 | 0.748 | 0.02 | 0.780 | 0.10 | 0.325 | -0.14 | 0.168 | 0.12 | 0.161 |
| **FX.ST.R** | 0.19 | 3.3E-05 | 0.25 | 3.5E-04 | 0.43 | 1.8E-08 | -0.05 | 0.586 | 0.11 | 0.274 | -0.03 | 0.795 | 0.18 | 0.035 |
| **PCR.L** | 0.28 | 2.9E-10 | 0.44 | 2.7E-10 | 0.30 | 9.1E-05 | 0.18 | 0.044 | 0.21 | 0.042 | 0.21 | 0.040 | 0.25 | 0.003 |
| **PCR.R** | 0.27 | 2.6E-09 | 0.27 | 8.2E-05 | 0.44 | 1.0E-08 | 0.20 | 0.020 | 0.14 | 0.179 | 0.23 | 0.020 | 0.25 | 0.003 |
| **PLIC.L** | 0.12 | 0.010 | 0.27 | 1.2E-04 | 0.19 | 0.014 | 0.10 | 0.246 | 0.08 | 0.442 | -0.20 | 0.045 | 0.04 | 0.625 |
| **PLIC.R** | 0.15 | 7.2E-04 | 0.26 | 1.5E-04 | 0.27 | 3.0E-04 | 0.18 | 0.043 | 0.12 | 0.231 | -0.16 | 0.121 | 0.05 | 0.544 |
| **PTR.L** | 0.17 | 2.1E-04 | 0.26 | 1.7E-04 | 0.12 | 0.107 | 0.16 | 0.065 | 0.15 | 0.152 | 0.07 | 0.502 | 0.14 | 0.093 |
| **PTR.R** | 0.17 | 1.8E-04 | 0.20 | 0.004 | 0.24 | 0.002 | 0.11 | 0.192 | 0.22 | 0.034 | 0.12 | 0.223 | 0.07 | 0.392 |
| **RLIC.L** | 0.16 | 3.0E-04 | 0.37 | 7.1E-08 | 0.08 | 0.302 | 0.14 | 0.117 | 0.09 | 0.384 | -0.03 | 0.790 | 0.13 | 0.105 |
| **RLIC.R** | 0.13 | 0.004 | 0.21 | 0.002 | 0.22 | 0.004 | 0.08 | 0.349 | 0.07 | 0.492 | -0.11 | 0.283 | 0.09 | 0.291 |
| **SCR.L** | 0.27 | 1.5E-09 | 0.42 | 1.5E-09 | 0.32 | 3.1E-05 | 0.22 | 0.013 | 0.16 | 0.114 | 0.05 | 0.585 | 0.27 | 9.6E-04 |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **SCR.R** | 0.23 | 3.7E-07 | 0.27 | 7.4E-05 | 0.34 | 6.1E-06 | 0.21 | 0.018 | 0.10 | 0.311 | 0.04 | 0.666 | 0.26 | 0.002 |
| **SFO.L** | 0.11 | 0.013 | 0.22 | 0.002 | 0.16 | 0.036 | -0.01 | 0.938 | 0.00 | 1.000 | -0.04 | 0.676 | 0.15 | 0.073 |
| **SFO.R** | 0.18 | 7.3E-05 | 0.24 | 4.5E-04 | 0.23 | 0.003 | 0.11 | 0.188 | 0.10 | 0.311 | 0.08 | 0.431 | 0.18 | 0.033 |
| **SLF.L** | 0.29 | 9.8E-11 | 0.44 | 3.3E-10 | 0.29 | 1.5E-04 | 0.25 | 0.004 | 0.19 | 0.063 | 0.13 | 0.190 | 0.30 | 2.6E-04 |
| **SLF.R** | 0.36 | 1.7E-15 | 0.40 | 1.1E-08 | 0.46 | 1.9E-09 | 0.35 | 7.1E-05 | 0.30 | 0.004 | 0.18 | 0.075 | 0.37 | 8.8E-06 |
| **SS.L** | 0.31 | 4.4E-12 | 0.66 | 5.1E-21 | 0.27 | 3.5E-04 | 0.22 | 0.011 | 0.19 | 0.063 | -0.03 | 0.791 | 0.23 | 0.007 |
| **SS.R** | 0.32 | 1.5E-12 | 0.31 | 1.0E-05 | 0.67 | 3.1E-18 | 0.24 | 0.005 | 0.42 | 4.8E-05 | 0.02 | 0.830 | 0.16 | 0.060 |
| **TAP.L** | 0.14 | 0.002 | 0.21 | 0.003 | 0.25 | 7.9E-04 | 0.02 | 0.823 | 0.05 | 0.652 | 0.09 | 0.381 | 0.08 | 0.338 |
| **TAP.R** | 0.13 | 0.003 | 0.11 | 0.119 | 0.30 | 8.7E-05 | 0.04 | 0.666 | 0.05 | 0.597 | 0.11 | 0.293 | 0.10 | 0.235 |
| **UNC.L** | 0.22 | 8.0E-07 | 0.47 | 1.1E-11 | 0.10 | 0.170 | 0.21 | 0.017 | 0.11 | 0.272 | 0.00 | 0.961 | 0.21 | 0.013 |
| **UNC.R** | 0.29 | 1.3E-10 | 0.30 | 1.3E-05 | 0.62 | 8.8E-16 | 0.14 | 0.107 | 0.42 | 4.4E-05 | 0.04 | 0.713 | 0.12 | 0.130 |

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**Supplementary Table 6.** Effect sizes for RD differences between healthy controls and each syndrome.

| | All Epilepsies | | L TLE-HS | | R TLE-HS | | L TLE-NL | | R TLE-NL | | GGE | | ExE | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **ROI** | Cohen's d | P value | Cohen's d | P value | Cohen's d | P value | Cohen's d | P value | Cohen's d | P value | Cohen's d | P value | Cohen's d | P value |
| **AverageRD** | 0.47 | 1.2E-24 | 0.66 | 5.1E-21 | 0.70 | 7.3E-20 | 0.25 | 0.004 | 0.23 | 0.019 | 0.17 | 0.081 | 0.48 | 7.6E-09 |
| **BCC** | 0.31 | 4.6E-12 | 0.44 | 2.1E-10 | 0.56 | 2.4E-13 | 0.05 | 0.545 | 0.09 | 0.333 | 0.04 | 0.664 | 0.39 | 3.5E-06 |
| **GCC** | 0.21 | 2.1E-06 | 0.35 | 3.4E-07 | 0.39 | 2.5E-07 | -0.09 | 0.280 | 0.09 | 0.368 | 0.04 | 0.713 | 0.29 | 4.4E-04 |
| **SCC** | 0.10 | 0.024 | 0.13 | 0.064 | 0.26 | 5.4E-04 | -0.07 | 0.395 | -0.03 | 0.786 | -0.14 | 0.163 | 0.23 | 0.005 |
| **ACR.L** | 0.38 | 5.6E-17 | 0.57 | 1.9E-16 | 0.51 | 2.1E-11 | 0.14 | 0.104 | 0.13 | 0.200 | 0.26 | 0.009 | 0.42 | 3.6E-07 |
| **ACR.R** | 0.45 | 2.9E-23 | 0.52 | 8.0E-14 | 0.69 | 2.5E-19 | 0.27 | 0.002 | 0.24 | 0.015 | 0.36 | 3.4E-04 | 0.46 | 3.3E-08 |
| **ALIC.L** | 0.23 | 4.9E-07 | 0.39 | 1.6E-08 | 0.25 | 0.001 | 0.13 | 0.138 | 0.09 | 0.364 | 0.06 | 0.563 | 0.27 | 0.001 |
| **ALIC.R** | 0.24 | 8.3E-08 | 0.24 | 3.7E-04 | 0.43 | 1.6E-08 | 0.14 | 0.116 | 0.18 | 0.072 | 0.12 | 0.223 | 0.26 | 0.002 |
| **CGC.L** | 0.39 | 5.7E-18 | 0.69 | 1.1E-22 | 0.48 | 3.3E-10 | 0.19 | 0.031 | 0.21 | 0.029 | 0.09 | 0.361 | 0.37 | 8.5E-06 |
| **CGC.R** | 0.33 | 1.2E-13 | 0.46 | 2.0E-11 | 0.57 | 9.2E-14 | 0.14 | 0.114 | 0.21 | 0.033 | 0.03 | 0.782 | 0.36 | 1.2E-05 |
| **CGH.L** | 0.26 | 9.8E-09 | 0.67 | 7.4E-22 | 0.21 | 0.006 | 0.01 | 0.877 | 0.04 | 0.655 | -0.02 | 0.869 | 0.24 | 0.003 |
| **CGH.R** | 0.23 | 2.0E-07 | 0.24 | 5.7E-04 | 0.61 | 1.5E-15 | -0.03 | 0.699 | 0.24 | 0.016 | 0.02 | 0.830 | 0.16 | 0.056 |
| **CST.L** | 0.06 | 0.188 | 0.04 | 0.556 | 0.02 | 0.798 | 0.11 | 0.222 | 0.08 | 0.394 | -0.07 | 0.496 | 0.14 | 0.086 |
| **CST.R** | 0.05 | 0.232 | 0.08 | 0.221 | 0.06 | 0.409 | 0.04 | 0.687 | 0.02 | 0.831 | -0.12 | 0.210 | 0.15 | 0.063 |
| **EC.L** | 0.48 | 2.4E-26 | 0.83 | 6.5E-32 | 0.63 | 2.1E-16 | 0.33 | 1.8E-04 | 0.33 | 8.0E-04 | 0.12 | 0.208 | 0.38 | 3.9E-06 |
| **EC.R** | 0.52 | 1.2E-30 | 0.61 | 2.5E-18 | 0.84 | 1.8E-27 | 0.40 | 4.1E-06 | 0.50 | 4.0E-07 | 0.21 | 0.032 | 0.43 | 2.2E-07 |
| **FX.ST.L** | 0.24 | 1.1E-07 | 0.59 | 1.5E-17 | 0.12 | 0.113 | 0.11 | 0.227 | 0.13 | 0.168 | -0.05 | 0.611 | 0.21 | 0.010 |
| **FX.ST.R** | 0.26 | 1.3E-08 | 0.32 | 4.6E-06 | 0.52 | 7.0E-12 | 0.05 | 0.593 | 0.17 | 0.074 | 0.08 | 0.428 | 0.22 | 0.009 |
| **PCR.L** | 0.31 | 3.8E-12 | 0.45 | 9.0E-11 | 0.31 | 3.7E-05 | 0.22 | 0.011 | 0.19 | 0.053 | 0.31 | 0.002 | 0.29 | 5.1E-04 |
| **PCR.R** | 0.33 | 3.0E-13 | 0.36 | 1.7E-07 | 0.42 | 2.7E-08 | 0.26 | 0.003 | 0.17 | 0.083 | 0.39 | 1.1E-04 | 0.32 | 1.1E-04 |
| **PLIC.L** | 0.18 | 7.7E-05 | 0.27 | 9.7E-05 | 0.19 | 0.011 | 0.17 | 0.057 | 0.12 | 0.220 | -0.03 | 0.800 | 0.22 | 0.009 |
| **PLIC.R** | 0.21 | 3.6E-06 | 0.25 | 2.8E-04 | 0.30 | 8.2E-05 | 0.24 | 0.005 | 0.15 | 0.133 | -0.01 | 0.916 | 0.21 | 0.011 |
| **PTR.L** | 0.24 | 1.2E-07 | 0.36 | 1.8E-07 | 0.19 | 0.014 | 0.18 | 0.036 | 0.10 | 0.292 | 0.19 | 0.052 | 0.26 | 0.002 |
| **PTR.R** | 0.25 | 2.5E-08 | 0.28 | 5.8E-05 | 0.31 | 5.3E-05 | 0.17 | 0.047 | 0.16 | 0.104 | 0.29 | 0.003 | 0.21 | 0.010 |
| **RLIC.L** | 0.28 | 9.3E-10 | 0.51 | 2.8E-13 | 0.21 | 0.006 | 0.19 | 0.028 | 0.15 | 0.135 | 0.18 | 0.066 | 0.23 | 0.006 |
| **RLIC.R** | 0.24 | 1.6E-07 | 0.31 | 6.5E-06 | 0.33 | 1.8E-05 | 0.17 | 0.052 | 0.15 | 0.129 | 0.11 | 0.275 | 0.19 | 0.024 |
| **SCR.L** | 0.32 | 7.2E-13 | 0.40 | 5.3E-09 | 0.38 | 6.0E-07 | 0.24 | 0.006 | 0.19 | 0.057 | 0.21 | 0.034 | 0.38 | 4.4E-06 |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **SCR.R** | 0.31 | 5.6E-12 | 0.37 | 1.1E-07 | 0.40 | 1.8E-07 | 0.26 | 0.003 | 0.15 | 0.117 | 0.19 | 0.053 | 0.38 | 5.7E-06 |
| **SFO.L** | 0.17 | 1.2E-04 | 0.25 | 2.4E-04 | 0.27 | 4.0E-04 | 0.03 | 0.696 | -0.08 | 0.405 | 0.06 | 0.564 | 0.29 | 5.5E-04 |
| **SFO.R** | 0.21 | 2.1E-06 | 0.30 | 1.4E-05 | 0.30 | 8.4E-05 | 0.12 | 0.171 | -0.02 | 0.813 | 0.11 | 0.258 | 0.27 | 9.5E-04 |
| **SLF.L** | 0.40 | 5.0E-19 | 0.56 | 5.1E-16 | 0.45 | 4.5E-09 | 0.30 | 0.001 | 0.20 | 0.042 | 0.32 | 0.001 | 0.43 | 2.6E-07 |
| **SLF.R** | 0.48 | 4.7E-26 | 0.53 | 1.7E-14 | 0.62 | 4.1E-16 | 0.43 | 7.7E-07 | 0.30 | 0.002 | 0.37 | 1.9E-04 | 0.49 | 4.4E-09 |
| **SS.L** | 0.41 | 1.4E-19 | 0.79 | 5.1E-29 | 0.39 | 3.5E-07 | 0.28 | 0.001 | 0.21 | 0.035 | 0.11 | 0.249 | 0.31 | 1.9E-04 |
| **SS.R** | 0.43 | 3.7E-21 | 0.44 | 2.2E-10 | 0.76 | 6.8E-23 | 0.32 | 2.6E-04 | 0.44 | 9.1E-06 | 0.19 | 0.056 | 0.33 | 9.0E-05 |
| **TAP.L** | 0.14 | 0.002 | 0.22 | 0.002 | 0.27 | 4.0E-04 | -0.01 | 0.924 | -0.08 | 0.398 | 0.09 | 0.380 | 0.13 | 0.118 |
| **TAP.R** | 0.15 | 9.0E-04 | 0.14 | 0.043 | 0.27 | 3.7E-04 | 0.04 | 0.673 | 0.02 | 0.869 | 0.18 | 0.070 | 0.16 | 0.051 |
| **UNC.L** | 0.29 | 1.2E-10 | 0.47 | 9.7E-12 | 0.27 | 3.4E-04 | 0.24 | 0.006 | 0.20 | 0.044 | 0.06 | 0.574 | 0.32 | 1.5E-04 |
| **UNC.R** | 0.33 | 4.8E-13 | 0.33 | 1.1E-06 | 0.72 | 6.4E-21 | 0.09 | 0.282 | 0.35 | 4.0E-04 | -0.01 | 0.934 | 0.28 | 6.3E-04 |

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**Supplementary Table 7.** Effect sizes for AD differences between healthy controls and each syndrome.

| | All Epilepsies | | L TLE-HS | | R TLE-HS | | L TLE-NL | | R TLE-NL | | GGE | | ExE | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **ROI** | Cohen's d | P value | Cohen's d | P value | Cohen's d | P value | Cohen's d | P value | Cohen's d | P value | Cohen's d | P value | Cohen's d | P value |
| **AverageAD** | 0.01 | 0.816 | 0.17 | 0.013 | 0.16 | 0.034 | -0.06 | 0.491 | -0.13 | 0.216 | -0.19 | 0.048 | -0.16 | 0.047 |
| **BCC** | 0.00 | 0.930 | 0.10 | 0.135 | 0.09 | 0.247 | -0.04 | 0.615 | -0.03 | 0.756 | -0.20 | 0.038 | -0.12 | 0.142 |
| **GCC** | 0.06 | 0.157 | 0.18 | 0.007 | 0.17 | 0.023 | -0.03 | 0.705 | -0.02 | 0.834 | -0.09 | 0.369 | -0.05 | 0.567 |
| **SCC** | 0.06 | 0.190 | 0.14 | 0.038 | 0.10 | 0.191 | -0.08 | 0.372 | -0.10 | 0.347 | 0.06 | 0.512 | 0.06 | 0.440 |
| **ACR.L** | 0.16 | 4.4E-04 | 0.29 | 1.9E-05 | 0.24 | 0.001 | 0.09 | 0.275 | 0.03 | 0.754 | 0.04 | 0.699 | 0.03 | 0.686 |
| **ACR.R** | 0.17 | 1.5E-04 | 0.22 | 0.001 | 0.35 | 2.0E-06 | 0.11 | 0.193 | 0.09 | 0.385 | 0.07 | 0.474 | 0.00 | 1.000 |
| **ALIC.L** | -0.04 | 0.312 | 0.06 | 0.338 | 0.01 | 0.869 | 0.01 | 0.928 | 0.00 | 1.000 | -0.29 | 0.003 | -0.23 | 0.004 |
| **ALIC.R** | -0.03 | 0.536 | 0.05 | 0.480 | 0.06 | 0.407 | 0.03 | 0.729 | 0.03 | 0.745 | -0.23 | 0.022 | -0.23 | 0.004 |
| **CGC.L** | -0.17 | 1.7E-04 | -0.15 | 0.023 | -0.31 | 2.7E-05 | 0.03 | 0.718 | -0.13 | 0.207 | -0.22 | 0.025 | -0.16 | 0.047 |
| **CGC.R** | -0.11 | 0.013 | -0.11 | 0.091 | -0.18 | 0.013 | 0.02 | 0.853 | -0.13 | 0.202 | -0.21 | 0.031 | -0.04 | 0.611 |
| **CGH.L** | -0.01 | 0.884 | 0.13 | 0.065 | -0.04 | 0.570 | -0.05 | 0.555 | -0.07 | 0.519 | -0.14 | 0.142 | -0.03 | 0.751 |
| **CGH.R** | 0.01 | 0.862 | 0.09 | 0.187 | -0.02 | 0.807 | -0.01 | 0.943 | 0.06 | 0.530 | -0.16 | 0.106 | -0.03 | 0.703 |
| **CST.L** | 0.04 | 0.340 | 0.09 | 0.196 | 0.03 | 0.636 | 0.11 | 0.214 | 0.06 | 0.526 | -0.08 | 0.393 | 0.00 | 1.000 |
| **CST.R** | 0.04 | 0.373 | 0.08 | 0.225 | 0.03 | 0.722 | 0.17 | 0.053 | -0.04 | 0.685 | -0.08 | 0.412 | 0.03 | 0.671 |
| **EC.L** | 0.06 | 0.167 | 0.23 | 0.001 | 0.02 | 0.795 | 0.07 | 0.409 | 0.17 | 0.091 | -0.17 | 0.091 | -0.11 | 0.186 |
| **EC.R** | 0.08 | 0.086 | 0.13 | 0.063 | 0.10 | 0.186 | 0.10 | 0.249 | 0.27 | 0.008 | -0.14 | 0.139 | -0.04 | 0.664 |
| **FX.ST.L** | -0.03 | 0.543 | 0.10 | 0.162 | -0.12 | 0.110 | -0.08 | 0.331 | 0.05 | 0.630 | -0.16 | 0.098 | -0.03 | 0.689 |
| **FX.ST.R** | 0.03 | 0.445 | 0.07 | 0.295 | 0.15 | 0.044 | -0.07 | 0.399 | -0.05 | 0.611 | -0.12 | 0.203 | 0.05 | 0.505 |
| **PCR.L** | 0.15 | 0.001 | 0.24 | 3.7E-04 | 0.21 | 0.005 | 0.10 | 0.262 | 0.08 | 0.406 | 0.02 | 0.870 | 0.14 | 0.090 |
| **PCR.R** | 0.19 | 2.8E-05 | 0.15 | 0.023 | 0.41 | 4.9E-08 | 0.14 | 0.101 | 0.11 | 0.290 | 0.04 | 0.714 | 0.14 | 0.086 |
| **PLIC.L** | -0.01 | 0.750 | 0.07 | 0.274 | 0.00 | 1.000 | 0.07 | 0.409 | 0.01 | 0.895 | -0.29 | 0.004 | -0.10 | 0.239 |
| **PLIC.R** | 0.05 | 0.296 | 0.13 | 0.050 | 0.10 | 0.159 | 0.18 | 0.035 | 0.02 | 0.833 | -0.27 | 0.006 | -0.06 | 0.484 |
| **PTR.L** | 0.03 | 0.470 | 0.12 | 0.085 | 0.04 | 0.626 | -0.01 | 0.865 | 0.07 | 0.468 | -0.12 | 0.219 | 0.00 | 1.000 |
| **PTR.R** | 0.01 | 0.803 | 0.02 | 0.780 | 0.08 | 0.274 | 0.02 | 0.791 | 0.09 | 0.363 | -0.13 | 0.190 | -0.08 | 0.338 |
| **RLIC.L** | 0.01 | 0.872 | 0.11 | 0.111 | -0.01 | 0.853 | 0.03 | 0.744 | -0.03 | 0.800 | -0.21 | 0.035 | 0.01 | 0.918 |
| **RLIC.R** | 0.08 | 0.057 | 0.11 | 0.104 | 0.18 | 0.015 | 0.12 | 0.159 | 0.00 | 1.000 | -0.14 | 0.149 | 0.06 | 0.487 |
| **SCR.L** | 0.11 | 0.012 | 0.28 | 3.2E-05 | 0.08 | 0.298 | 0.15 | 0.084 | 0.07 | 0.478 | -0.09 | 0.335 | 0.03 | 0.742 |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **SCR.R** | 0.14 | 0.002 | 0.17 | 0.013 | 0.29 | 1.2E-04 | 0.18 | 0.042 | -0.03 | 0.780 | 0.02 | 0.861 | 0.09 | 0.274 |
| **SFO.L** | 0.02 | 0.579 | 0.09 | 0.181 | 0.03 | 0.691 | 0.00 | 1.000 | 0.02 | 0.847 | -0.08 | 0.442 | -0.02 | 0.825 |
| **SFO.R** | 0.05 | 0.257 | 0.10 | 0.128 | 0.06 | 0.451 | 0.05 | 0.539 | 0.15 | 0.155 | -0.03 | 0.786 | -0.07 | 0.398 |
| **SLF.L** | 0.02 | 0.718 | 0.07 | 0.274 | -0.04 | 0.550 | 0.09 | 0.290 | -0.02 | 0.877 | -0.13 | 0.198 | 0.05 | 0.535 |
| **SLF.R** | 0.07 | 0.107 | 0.10 | 0.144 | 0.06 | 0.430 | 0.15 | 0.091 | 0.06 | 0.563 | -0.08 | 0.428 | 0.10 | 0.223 |
| **SS.L** | 0.09 | 0.039 | 0.34 | 6.6E-07 | 0.01 | 0.932 | 0.07 | 0.427 | -0.03 | 0.765 | -0.14 | 0.145 | 0.06 | 0.448 |
| **SS.R** | 0.12 | 0.005 | 0.04 | 0.542 | 0.44 | 4.3E-09 | 0.09 | 0.283 | 0.22 | 0.035 | -0.09 | 0.346 | -0.01 | 0.885 |
| **TAP.L** | 0.08 | 0.092 | 0.09 | 0.174 | 0.09 | 0.243 | 0.02 | 0.809 | 0.17 | 0.089 | 0.05 | 0.618 | 0.04 | 0.632 |
| **TAP.R** | 0.06 | 0.195 | 0.00 | 1.000 | 0.16 | 0.031 | 0.04 | 0.630 | 0.08 | 0.429 | 0.02 | 0.860 | 0.02 | 0.800 |
| **UNC.L** | 0.03 | 0.509 | 0.15 | 0.031 | -0.09 | 0.250 | 0.08 | 0.372 | 0.02 | 0.813 | 0.01 | 0.916 | -0.07 | 0.365 |
| **UNC.R** | 0.13 | 0.003 | 0.18 | 0.007 | 0.15 | 0.037 | 0.19 | 0.025 | 0.21 | 0.038 | 0.08 | 0.408 | -0.04 | 0.602 |

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**Supplementary Table 8. Relationship between FA and age of disease onset by syndrome**. Partial correlations between FA in each ROI and age of disease onset controlling for age, age$^2$ and sex. Results are split by syndrome: all syndromes (All), temporal lobe epilepsy with hippocampal sclerosis in the left and right hemisphere (TLE-HS-l and TLE-HS-r respectively), non-lesional temporal lobe epilepsy in the left and right hemisphere (TLE-NL-l and TLE-NL-r respectively), genetic generalized epilepsy (GGE) and extra temporal (ExE). ROIs are separated by left (.L) and right (.R) hemisphere where indicated. Significance was set at *** $p$ =< 0.001 (controlling for multiple comparisons, one sided). * $p < 0.05$ ** $p < 0.01$ *** $p$ =< 0.001.

| ROI | All | TLE-HS-l | TLE-HS-r | TLE-NL-l | TLE-NL-r | GGE | ExE |
|---|---|---|---|---|---|---|---|
| **AverageFA** | .19*** | .20*** | .24*** | .08 | .14 | .08 | .02 |
| **BCC** | .15*** | .19*** | .24*** | .08 | .00 | -.05 | .03 |
| **GCC** | .16*** | .20*** | .19** | .06 | .09 | -.06 | .05 |
| **SCC** | .13*** | .11* | .28*** | .02 | -.09 | .00 | .11 |
| **ACR.L** | .13*** | .18** | .16** | .03 | .07 | -.03 | .02 |
| **ACR.R** | .11*** | .12* | .07 | .13 | .15 | -.02 | .00 |
| **ALIC.L** | .09** | .08 | .12* | .02 | .16 | -.04 | -.03 |
| **ALIC.R** | .11*** | .15** | .10 | .12 | .11 | .02 | -.01 |
| **CGC.L** | .16*** | .17** | .15* | .17* | .08 | .01 | .01 |
| **CGC.R** | .16*** | .17** | .19** | .14* | .11 | .09 | -.01 |
| **CGH.L** | .11*** | .08 | .22*** | -.03 | -.12 | .11 | .06 |
| **CGH.R** | .12*** | -.03 | .27*** | .09 | .12 | .11 | -.01 |
| **CST.L** | .06* | .07 | .07 | .07 | .04 | .11 | -.01 |
| **CST.R** | .03 | .03 | -.01 | .01 | .09 | .03 | -.01 |
| **EC.L** | .16*** | .20*** | .19** | .08 | .13 | .08 | -.05 |
| **EC.R** | .17*** | .17** | .25*** | .07 | .15 | .16* | .00 |
| **FX.ST.L** | .11*** | .12* | .13* | .09 | .02 | .00 | .01 |
| **FX.ST.R** | .13*** | .14** | .19** | .09 | .06 | .07 | -.03 |
| **PCR.L** | .09** | .10* | .15* | .05 | -.11 | .07 | .02 |
| **PCR.R** | .13*** | .11* | .22*** | .06 | -.08 | .05 | .07 |
| **PLIC.L** | .03 | .03 | .04 | -.01 | -.03 | -.05 | .06 |
| **PLIC.R** | .05 | .05 | .06 | -.01 | -.07 | .07 | .05 |
| **PTR.L** | .11*** | .16** | .13* | .11 | -.02 | .03 | .02 |
| **PTR.R** | .10*** | .12* | .14* | .11 | -.04 | .01 | .00 |
| **RLIC.L** | .10*** | .14* | .09 | .05 | -.02 | .04 | .08 |
| **RLIC.R** | .07* | .05 | .10 | .00 | .03 | .05 | -.03 |
| **SCR.L** | .07** | .11* | .08 | -.02 | .02 | -.03 | .07 |
| **SCR.R** | .09*** | .14* | .08 | -.01 | -.03 | .02 | .10 |
| **SFO.L** | .09** | .12* | .03 | .138* | .08 | -.01 | -.03 |
| **SFO.R** | .11*** | .15** | .08 | .08 | .08 | .08 | .02 |
| **SLF.L** | .13*** | .13* | .16** | .155* | -.01 | .01 | .05 |
| **SLF.R** | .14*** | .07 | .23*** | .16* | .04 | .11 | .05 |
| **SS.L** | .12*** | .16** | .15* | .06 | .00 | .02 | .08 |
| **SS.R** | .12*** | .12* | .17** | .13 | -.01 | .07 | .02 |
| **TAP.L** | .13*** | .11* | .18** | .09 | .07 | -.06 | .08 |
| **TAP.R** | .13*** | .09 | .19** | .02 | .10 | .00 | .06 |
| **UNC.L** | .08** | .13* | .09 | -.07 | .09 | .11 | -.06 |
| **UNC.R** | .15*** | .05 | .27*** | .05 | .30*** | .09 | .00 |

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**Supplementary Table 9. Relationship between FA and disease duration by syndrome**. Partial correlations between FA in each ROI and disease duration controlling for age, age$^2$ and sex. Results are split by syndrome: all syndromes (All), temporal lobe epilepsy with hippocampal sclerosis in the left and right hemisphere (TLE-HS-l and TLE-HS-r respectively), non-lesional temporal lobe epilepsy in the left and right hemisphere (TLE-NL-l and TLE-NL-r respectively), genetic generalized epilepsy (GGE) and extra temporal (Extra). ROIs are separated by left (.L) and right (.R) hemisphere where indicated. Significance was set at *** $p$ =< 0.001 (controlling for multiple comparisons, one sided). * $p < 0.05$ ** $p < 0.01$ *** $p$ =< 0.001.

| ROI | All | TLE-HS-l | TLE-HS-r | TLE-NL-l | TLE-NL-r | GGE | ExE |
|---|---|---|---|---|---|---|---|
| **AverageFA** | -.17*** | -.17** | -.21*** | -.09 | -.23* | -.09 | -.02 |
| **BCC** | -.16*** | -.21*** | -.20** | -.15* | -.13 | .04 | -.03 |
| **GCC** | -.13*** | -.16** | -.18** | -.06 | -.15 | .02 | -.05 |
| **SCC** | -.10*** | -.06 | -.22*** | -.01 | .01 | -.01 | -.11 |
| **ACR.L** | -.11*** | -.14* | -.13* | -.06 | -.16 | .00 | -.01 |
| **ACR.R** | -.10*** | -.09 | -.05 | -.15* | -.25** | -.01 | .02 |
| **ALIC.L** | -.08** | -.08 | -.09 | -.04 | -.23* | .06 | .04 |
| **ALIC.R** | -.09** | -.10 | -.09 | -.14* | -.19* | -.02 | .06 |
| **CGC.L** | -.17** | -.20*** | -.11 | -.22** | -.16 | .01 | -.02 |
| **CGC.R** | -.17*** | -.20*** | -.14* | -.19* | -.21* | -.06 | .00 |
| **CGH.L** | -.09** | -.03 | -.13* | -.01 | .05 | -.10 | -.03 |
| **CGH.R** | -.10** | .06 | -.28*** | -.07 | -.08 | -.09 | .03 |
| **CST.L** | -.05 | -.02 | -.12* | -.05 | -.13 | -.11 | .04 |
| **CST.R** | -.01 | -.03 | .01 | .04 | -.12 | -.04 | .08 |
| **EC.L** | -.16** | -.22*** | -.13* | -.10 | -.17 | -.07 | .05 |
| **EC.R** | -.16** | -.15** | -.22*** | -.10 | -.19* | -.17* | -.01 |
| **FX.ST.L** | -.09** | -.11* | -.02 | -.12 | -.05 | -.01 | -.03 |
| **FX.ST.R** | -.13** | -.15** | -.12* | -.11 | -.09 | -.07 | -.01 |
| **PCR.L** | -.06* | -.04 | -.11 | .01 | .03 | -.07 | -.02 |
| **PCR.R** | -.10*** | -.03 | -.26*** | .00 | .01 | -.09 | -.07 |
| **PLIC.L** | -.03 | -.02 | -.06 | .01 | -.06 | .07 | -.05 |
| **PLIC.R** | -.04 | -.02 | -.06 | -.03 | .01 | -.07 | -.01 |
| **PTR.L** | -.09** | -.12* | -.14* | -.07 | -.06 | -.07 | -.03 |
| **PTR.R** | -.08** | -.09 | -.14* | -.06 | -.05 | -.07 | -.02 |
| **RLIC.L** | -.08** | -.13* | -.04 | -.10 | -.05 | -.04 | -.04 |
| **RLIC.R** | -.05* | -.03 | -.09 | -.03 | -.10 | -.05 | .07 |
| **SCR.L** | -.06* | -.09 | -.09 | .04 | -.06 | .03 | -.02 |
| **SCR.R** | -.09** | -.10* | -.15* | .00 | .02 | -.03 | -.06 |
| **SFO.L** | -.06* | -.10 | .02 | -.11 | -.08 | .02 | .01 |
| **SFO.R** | -.09** | -.12* | -.09 | -.12 | -.04 | -.09 | .02 |
| **SLF.L** | -.13*** | -.12* | -.12* | -.14 | -.07 | .00 | -.07 |
| **SLF.R** | -.12*** | -.05 | -.20** | -.14* | -.07 | -.10 | -.05 |
| **SS.L** | -.12*** | -.15** | -.09 | -.07 | -.16 | -.03 | -.09 |
| **SS.R** | -.11*** | -.07 | -.18** | -.13 | -.09 | -.09 | -.01 |
| **TAP.L** | -.14*** | -.08 | -.26*** | -.05 | -.16 | .05 | -.10 |
| **TAP.R** | -.13*** | -.03 | -.26*** | -.02 | -.12 | -.03 | -.08 |
| **UNC.L** | -.07** | -.15** | -.02 | .10 | -.07 | -.12 | .03 |
| **UNC.R** | -.14** | -.05 | -.24*** | -.01 | -.37*** | -.09 | -.05 |

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**Supplementary Table 10. Relationship between MD and age of disease onset by syndrome**. Partial correlations between MD in each ROI and age of disease onset controlling for age, age$^2$ and sex. Results are split by syndrome: all syndromes (All), temporal lobe epilepsy with hippocampal sclerosis in the left and right hemisphere (TLE-HS-l and TLE-HS-r respectively), non-lesional temporal lobe epilepsy in the left and right hemisphere (TLE-NL-l and TLE-NL-r respectively), genetic generalized epilepsy (GGE) and extra temporal (Extra). ROIs are separated by left (.L) and right (.R) hemisphere where indicated. Significance was set at *** $p =< 0.001$ (controlling for multiple comparisons, one sided). * $p < 0.05$ ** $p < 0.01$ *** $p =< 0.001$.

| ROI | All | TLE-HS-l | TLE-HS-r | TLE-NL-l | TLE-NL-r | GGE | ExE |
|---|---|---|---|---|---|---|---|
| **AverageMD** | -.16*** | -.11* | -.27*** | -.14* | -.09 | -.02 | .00 |
| **BCC** | -.13*** | -.08 | -.20** | -.06 | -.10 | .03 | -.02 |
| **GCC** | -.10*** | -.12* | -.10 | -.02 | -.05 | .06 | -.03 |
| **SCC** | -.11*** | -.08 | -.21*** | -.02 | -.08 | -.10 | .04 |
| **ACR.L** | -.10*** | -.14** | -.11* | .02 | -.05 | .03 | -.05 |
| **ACR.R** | -.10** | -.05 | -.11 | -.03 | -.06 | .05 | -.09 |
| **ALIC.L** | -.07* | -.08 | -.04 | -.04 | .06 | .04 | -.08 |
| **ALIC.R** | -.08** | -.09 | -.05 | -.04 | .14 | .02 | -.13 |
| **CGC.L** | -.11*** | -.11* | -.07 | -.10 | -.04 | -.10 | -.06 |
| **CGC.R** | -.10*** | .00 | -.11 | -.15* | -.04 | -.10 | -.12 |
| **CGH.L** | -.08** | -.10 | -.15* | -.02 | .14 | .03 | -.05 |
| **CGH.R** | -.10*** | -.01 | -.23*** | -.05 | .02 | -.05 | -.01 |
| **CST.L** | -.03 | -.05 | -.13* | -.01 | .14 | .04 | .02 |
| **CST.R** | -.01 | .01 | -.13* | .08 | .13 | .02 | .03 |
| **EC.L** | -.09*** | -.06 | -.11 | -.04 | .01 | -.06 | -.03 |
| **EC.R** | -.10*** | -.08 | -.14* | -.01 | .06 | -.05 | -.12 |
| **FX.ST.L** | -.08** | -.04 | -.15* | -.13 | .00 | .04 | -.02 |
| **FX.ST.R** | -.11*** | .00 | -.20*** | -.12 | -.01 | .05 | -.08 |
| **PCR.L** | -.08** | -.02 | -.15* | .03 | -.06 | -.05 | -.02 |
| **PCR.R** | -.09** | -.04 | -.17** | .02 | -.07 | -.04 | -.01 |
| **PLIC.L** | -.03 | .02 | -.03 | -.08 | .05 | .12 | -.18* |
| **PLIC.R** | -.05 | .01 | -.06 | -.09 | .13 | .03 | -.12 |
| **PTR.L** | -.08** | -.05 | -.19** | .04 | .02 | .01 | -.06 |
| **PTR.R** | -.07* | -.04 | -.13* | .05 | -.03 | .00 | -.01 |
| **RLIC.L** | -.10*** | -.08 | -.10 | -.06 | -.07 | -.07 | -.11 |
| **RLIC.R** | -.09** | .02 | -.19** | .00 | -.06 | -.02 | -.09 |
| **SCR.L** | -.065* | -.05 | -.13* | .06 | -.02 | .07 | -.08 |
| **SCR.R** | -.064* | -.05 | -.08 | .03 | .09 | .06 | -.12 |
| **SFO.L** | -.04 | .00 | -.06 | -.02 | .05 | .15 | -.07 |
| **SFO.R** | -.06* | .02 | -.10 | -.01 | .00 | .08 | -.14* |
| **SLF.L** | -.07** | -.06 | -.11 | .01 | .07 | -.04 | -.05 |
| **SLF.R** | -.07* | -.05 | -.10 | -.04 | .12 | -.01 | -.06 |
| **SS.L** | -.10*** | -.14** | -.15* | .05 | .10 | -.01 | -.07 |
| **SS.R** | -.10*** | -.02 | -.22*** | .06 | -.02 | -.01 | -.04 |
| **TAP.L** | -.12*** | -.15** | -.22*** | .02 | -.10 | -.03 | .05 |
| **TAP.R** | -.10*** | -.05 | -.16** | -.16* | -.17* | -.01 | .08 |
| **UNC.L** | -.06* | -.11* | -.04 | .06 | .07 | -.23** | .06 |
| **UNC.R** | -.09** | .01 | -.20*** | .07 | -.02 | -.01 | -.09 |

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**Supplementary Table 11. Relationship between MD and disease duration by syndrome**. Partial correlations between MD in each ROI and disease duration controlling for age, age$^2$ and sex. Results are split by syndrome: all syndromes (All), temporal lobe epilepsy with hippocampal sclerosis in the left and right hemisphere (TLE-HS-l and TLE-HS-r respectively), non-lesional temporal lobe epilepsy in the left and right hemisphere (TLE-NL-l and TLE-NL-r respectively), genetic generalized epilepsy (GGE) and extra temporal (Extra). ROIs are separated by left (.L) and right (.R) hemisphere where indicated. Significance was set at *** $p$ =< 0.001 (controlling for multiple comparisons, one sided). * $p < 0.05$ ** $p < 0.01$ *** $p$ =< 0.001.

| ROI | All | TLE-HS-l | TLE-HS-r | TLE-NL-l | TLE-NL-r | GGE | ExE |
|---|---|---|---|---|---|---|---|
| **AverageMD** | .16*** | .12* | .26*** | .14* | .05 | .00 | .05 |
| **BCC** | .13*** | .09 | .18** | .11 | .06 | -.04 | .04 |
| **GCC** | .11*** | .16** | .12* | -.04 | .00 | -.07 | .07 |
| **SCC** | .09** | .05 | .21*** | .02 | -.04 | .09 | -.02 |
| **ACR.L** | .11*** | .15** | .17** | -.07 | .02 | -.05 | .06 |
| **ACR.R** | .10*** | .06 | .16* | -.03 | .03 | -.07 | .09 |
| **ALIC.L** | .03 | .03 | -.03 | .02 | -.13 | -.06 | .12 |
| **ALIC.R** | .04 | .05 | -.01 | -.01 | -.18* | -.04 | .16* |
| **CGC.L** | .08** | .06 | .06 | .03 | .06 | .08 | .07 |
| **CGC.R** | .09** | -.01 | .13* | .09 | .03 | .08 | .15* |
| **CGH.L** | .06* | .03 | .14* | -.02 | -.10 | -.03 | .06 |
| **CGH.R** | .09** | -.03 | .26*** | .04 | .06 | .05 | .02 |
| **CST.L** | .00 | -.02 | .14* | .01 | -.18* | -.03 | .01 |
| **CST.R** | -.02 | -.03 | .10 | -.10 | -.21* | -.01 | .00 |
| **EC.L** | .08** | .07 | .08 | -.03 | -.01 | .03 | .08 |
| **EC.R** | .09** | .03 | .15* | -.01 | .00 | .03 | .17* |
| **FX.ST.L** | .05* | .03 | .12* | .06 | -.03 | -.07 | -.02 |
| **FX.ST.R** | .10*** | -.02 | .18** | .05 | .12 | -.07 | .11 |
| **PCR.L** | .08** | .04 | .16** | -.06 | -.03 | .04 | .04 |
| **PCR.R** | .09** | .03 | .17** | .03 | -.04 | .02 | .02 |
| **PLIC.L** | .00 | -.06 | -.03 | .05 | -.06 | -.14 | .19** |
| **PLIC.R** | .04 | -.02 | .01 | .13 | -.11 | -.07 | .14* |
| **PTR.L** | .09** | .07 | .21*** | -.04 | -.10 | -.01 | .07 |
| **PTR.R** | .06* | .04 | .13* | -.05 | -.02 | .00 | -.01 |
| **RLIC.L** | .09** | .06 | .12* | .05 | .07 | .06 | .14* |
| **RLIC.R** | .09** | -.01 | .17** | -.01 | .06 | .01 | .13 |
| **SCR.L** | .06* | .03 | .13* | -.07 | .02 | -.09 | .08 |
| **SCR.R** | .05* | .03 | .09 | -.09 | -.05 | -.07 | .12 |
| **SFO.L** | .03 | .03 | .03 | -.05 | .00 | -.16* | .08 |
| **SFO.R** | .070* | .03 | .11 | -.04 | .00 | -.09 | .13 |
| **SLF.L** | .07** | .03 | .11 | -.02 | .03 | .02 | .09 |
| **SLF.R** | .06* | .02 | .10 | .02 | -.07 | -.01 | .10 |
| **SS.L** | .11*** | .18** | .139* | -.10 | -.03 | .00 | .11 |
| **SS.R** | .11*** | .03 | .24*** | -.12 | .07 | .01 | .07 |
| **TAP.L** | .13*** | .14* | .29*** | -.04 | -.05 | .03 | .02 |
| **TAP.R** | .09** | .05 | .20** | .09 | -.02 | .00 | -.05 |
| **UNC.L** | .05 | .10 | .03 | -.12 | -.05 | .23** | -.06 |
| **UNC.R** | .08** | .03 | .12* | -.12 | .13 | -.01 | .12 |

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**Supplementary Table 12. Relationship between RD and age of disease onset by syndrome**. Partial correlations between RD in each ROI and age of disease onset controlling for age, age$^2$ and sex. Results are split by syndrome: all syndromes (All), temporal lobe epilepsy with hippocampal sclerosis in the left and right hemisphere (TLE-HS-l and TLE-HS-r respectively), non-lesional temporal lobe epilepsy in the left and right hemisphere (TLE-NL-l and TLE-NL-r respectively), genetic generalized epilepsy (GGE) and extra temporal (Extra). ROIs are separated by left (.L) and right (.R) hemisphere where indicated. Significance was set at *** $p$ =< 0.001 (controlling for multiple comparisons, one sided). * $p < 0.05$ ** $p < 0.01$ *** $p$ =< 0.001.

| ROI | All | TLE-HS-l | TLE-HS-r | TLE-NL-l | TLE-NL-r | GGE | ExE |
|---|---|---|---|---|---|---|---|
| **AverageRD** | -.18*** | -.15** | -.25*** | -.14* | -.18* | -.05 | -.02 |
| **BCC** | -.17*** | -.12* | -.24*** | -.15* | -.19* | .03 | -.03 |
| **GCC** | -.13*** | -.16*** | -.14* | -.05 | -.11 | .01 | -.03 |
| **SCC** | -.14*** | -.08 | -.27*** | -.02 | -.16 | -.06 | -.08 |
| **ACR.L** | -.13*** | -.17*** | -.12* | .00 | -.14 | .00 | -.05 |
| **ACR.R** | -.11*** | -.07 | -.09 | -.06 | -.16* | .01 | -.07 |
| **ALIC.L** | -.09*** | -.09 | -.11* | -.04 | -.03 | .07 | -.06 |
| **ALIC.R** | -.12*** | -.08 | -.10 | -.11 | -.08 | -.03 | -.11 |
| **CGC.L** | -.14*** | -.14** | -.11* | -.10 | -.06 | -.05 | -.04 |
| **CGC.R** | -.13*** | -.04 | -.14* | -.14* | -.11 | -.12 | -.05 |
| **CGH.L** | -.13*** | -.14** | -.18** | -.06 | .09 | -.03 | -.07 |
| **CGH.R** | -.12*** | -.02 | -.24*** | -.13 | -.05 | -.09 | .00 |
| **CST.L** | -.05* | -.12* | -.10 | -.04 | .08 | .01 | -.01 |
| **CST.R** | -.04 | -.05 | -.08 | -.04 | .06 | .03 | -.02 |
| **EC.L** | -.14*** | -.14** | -.15* | -.08 | -.08 | -.09 | -.01 |
| **EC.R** | -.14*** | -.12* | -.20** | -.06 | -.06 | -.10 | -.08 |
| **FX.ST.L** | -.12*** | -.10* | -.11* | -.21** | -.01 | .01 | -.02 |
| **FX.ST.R** | -.13*** | -.07 | -.18** | -.17* | -.08 | -.05 | -.03 |
| **PCR.L** | -.10 | -.02 | -.16** | -.03 | -.08 | -.10 | -.03 |
| **PCR.R** | -.11*** | -.08 | -.19** | .02 | -.07 | -.07 | -.05 |
| **PLIC.L** | -.05 | .03 | -.09 | -.06 | -.02 | .07 | -.13 |
| **PLIC.R** | -.08** | -.01 | -.10 | -.11 | .01 | -.04 | -.07 |
| **PTR.L** | -.12*** | -.10* | -.20** | -.03 | -.11 | -.05 | -.06 |
| **PTR.R** | -.11*** | -.10 | -.15* | .03 | -.14 | -.03 | -.02 |
| **RLIC.L** | -.13*** | -.10* | -.14* | -.10 | -.12 | -.08 | -.14* |
| **RLIC.R** | -.11*** | -.02 | -.17** | -.04 | -.09 | -.04 | -.06 |
| **SCR.L** | -.07* | -.06 | -.10 | .05 | -.09 | .06 | -.10 |
| **SCR.R** | -.08** | -.07 | -.07 | .03 | .05 | .01 | -.15* |
| **SFO.L** | -.09** | -.07 | -.11 | .00 | -.07 | .12 | -.04 |
| **SFO.R** | -.11*** | -.04 | -.15* | -.07 | .02 | .01 | -.10 |
| **SLF.L** | -.11*** | -.08 | -.15* | -.03 | .05 | -.05 | -.05 |
| **SLF.R** | -.10*** | -.03 | -.14* | -.04 | .02 | -.08 | -.07 |
| **SS.L** | -.14*** | -.17** | -.17** | -.01 | -.05 | -.05 | -.10 |
| **SS.R** | -.12*** | -.08 | -.21*** | .05 | -.16 | -.06 | -.02 |
| **TAP.L** | -.14*** | -.11* | -.24*** | .03 | -.16* | -.03 | -.01 |
| **TAP.R** | -.13*** | -.07 | -.19** | -.14* | -.21* | -.04 | .03 |
| **UNC.L** | -.07* | -.09 | -.05 | .04 | .03 | -.23** | .07 |
| **UNC.R** | -.12*** | -.05 | -.21*** | .02 | -.15 | -.02 | -.05 |

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**Supplementary Table 13. Relationship between RD and disease duration by syndrome**. Partial correlations between RD in each ROI and disease duration controlling for age, age$^2$ and sex. Results are split by syndrome: all syndromes (All), temporal lobe epilepsy with hippocampal sclerosis in the left and right hemisphere (TLE-HS-l and TLE-HS-r respectively), non-lesional temporal lobe epilepsy in the left and right hemisphere (TLE-NL-l and TLE-NL-r respectively), genetic generalized epilepsy (GGE) and extra temporal (Extra). ROIs are separated by left (.L) and right (.R) hemisphere where indicated. Significance was set at *** $p =< 0.001$ (controlling for multiple comparisons, one sided). * $p < 0.05$ ** $p < 0.01$ *** $p =< 0.001$.

| ROI | All | TLE-HS-l | TLE-HS-r | TLE-NL-l | TLE-NL-r | GGE | ExE |
|---|---|---|---|---|---|---|---|
| **AverageRD** | .19*** | .17** | .27*** | .15* | .16 | .04 | .05 |
| **BCC** | .18*** | .14* | .24*** | .21** | .15 | -.04 | .04 |
| **GCC** | .15*** | .21** | .18** | .00 | .08 | -.02 | .04 |
| **SCC** | .15*** | .09 | .29*** | .04 | .05 | .05 | .11 |
| **ACR.L** | .14*** | .19** | .18** | -.03 | .11 | -.01 | .06 |
| **ACR.R** | .11*** | .09 | .13* | .01 | .16 | -.03 | .06 |
| **ALIC.L** | .07* | .07 | .05 | -.01 | .06 | -.09 | .09 |
| **ALIC.R** | .09** | .08 | .08 | .04 | .07 | .01 | .11 |
| **CGC.L** | .14*** | .15** | .12* | .04 | .10 | .03 | .06 |
| **CGC.R** | .14*** | .04 | .18** | .10 | .11 | .10 | .07 |
| **CGH.L** | .11*** | .08 | .18** | .02 | -.06 | .03 | .08 |
| **CGH.R** | .12*** | -.02 | .28*** | .10 | .13 | .09 | .02 |
| **CST.L** | .03 | .09 | .13* | .00 | -.14 | -.01 | .01 |
| **CST.R** | .01 | .04 | .08 | .00 | -.16 | -.02 | .01 |
| **EC.L** | .14*** | .14* | .15* | .04 | .11 | .07 | .04 |
| **EC.R** | .14*** | .09 | .21*** | .04 | .10 | .09 | .12 |
| **FX.ST.L** | .10*** | .10 | .11 | .15* | .01 | -.01 | .02 |
| **FX.ST.R** | .14*** | .07 | .17** | .12 | .15 | .03 | .07 |
| **PCR.L** | .10** | .03 | .20** | -.02 | -.01 | .09 | .05 |
| **PCR.R** | .11*** | .07 | .21*** | -.01 | -.03 | .05 | .06 |
| **PLIC.L** | .02 | -.04 | .07 | -.05 | -.01 | -.08 | .15* |
| **PLIC.R** | .06* | .01 | .09 | .09 | -.06 | .02 | .06 |
| **PTR.L** | .13*** | .12* | .24*** | .02 | .02 | .05 | .07 |
| **PTR.R** | .11*** | .11* | .18** | -.06 | .12 | .03 | .01 |
| **RLIC.L** | .10*** | .06 | .16* | .02 | .05 | .07 | .13 |
| **RLIC.R** | .11*** | .04 | .17** | .02 | .08 | .03 | .06 |
| **SCR.L** | .07* | .06 | .13* | -.08 | .08 | -.08 | .07 |
| **SCR.R** | .08** | .07 | .08 | -.08 | -.03 | -.02 | .13 |
| **SFO.L** | .07* | .05 | .07 | -.03 | .06 | -.13 | .05 |
| **SFO.R** | .10*** | .06 | .11 | .06 | .04 | -.02 | .07 |
| **SLF.L** | .12*** | .08 | .17** | .04 | .05 | .04 | .09 |
| **SLF.R** | .10*** | .00 | .16* | .04 | .03 | .07 | .09 |
| **SS.L** | .15*** | .19*** | .17** | -.03 | .13 | .05 | .12 |
| **SS.R** | .14*** | .12* | .22*** | -.06 | .22* | .05 | .04 |
| **TAP.L** | .14*** | .12* | .32*** | -.11 | .03 | .04 | .08 |
| **TAP.R** | .13*** | .07 | .25*** | .07 | .08 | .04 | .01 |
| **UNC.L** | .07* | .12* | .05 | -.11 | -.02 | .24** | -.06 |
| **UNC.R** | .11*** | .00 | .20** | -.06 | .25** | .01 | .09 |

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**Supplementary Table 14. Relationship between AD and age of disease onset by syndrome**. Partial correlations between AD in each ROI and age of disease onset controlling for age, age$^2$ and sex. Results are split by syndrome: all syndromes (All), temporal lobe epilepsy with hippocampal sclerosis in the left and right hemisphere (TLE-HS-l and TLE-HS-r respectively), non-lesional temporal lobe epilepsy in the left and right hemisphere (TLE-NL-l and TLE-NL-r respectively), genetic generalized epilepsy (GGE) and extra temporal (Extra). ROIs are separated by left (.L) and right (.R) hemisphere where indicated. Significance was set at *** $p$ =< 0.001 (controlling for multiple comparisons, one sided). * $p$ < 0.05 ** $p$ < 0.01 *** $p$ =< 0.001.

| ROI | All | TLE-HS-l | TLE-HS-r | TLE-NL-l | TLE-NL-r | GGE | ExE |
|---|---|---|---|---|---|---|---|
| **AverageAD** | -.05* | -.03 | -.16** | -.01 | .09 | .05 | .03 |
| **BCC** | -.01 | .01 | .00 | -.03 | -.02 | .01 | .02 |
| **GCC** | -.02 | -.05 | .04 | -.03 | .06 | .08 | .00 |
| **SCC** | -.06* | -.08 | -.11 | .02 | -.07 | -.08 | .17* |
| **ACR.L** | -.02 | -.04 | -.01 | .04 | .10 | .06 | -.02 |
| **ACR.R** | -.04 | -.02 | -.08 | .04 | .11 | .09 | -.10 |
| **ALIC.L** | -.02 | -.04 | .01 | .00 | .11 | -.04 | -.07 |
| **ALIC.R** | -.01 | -.04 | .04 | .05 | .22* | .01 | -.13 |
| **CGC.L** | .05 | .03 | .02 | .04 | .16 | -.10 | -.01 |
| **CGC.R** | .05 | .12* | .03 | .00 | .16 | -.04 | -.10 |
| **CGH.L** | .00 | -.02 | -.04 | .04 | .14 | .09 | .00 |
| **CGH.R** | -.02 | -.01 | -.13* | .03 | .19* | .02 | -.02 |
| **CST.L** | .02 | .03 | -.10 | .05 | .15 | .02 | .04 |
| **CST.R** | .04 | .11* | -.09 | .12 | .17* | -.01 | .07 |
| **EC.L** | .01 | .01 | .02 | .02 | .19* | .02 | -.05 |
| **EC.R** | .03 | .05 | .06 | .03 | .26** | .05 | -.14* |
| **FX.ST.L** | -.03 | .00 | -.09 | -.10 | .05 | .05 | -.01 |
| **FX.ST.R** | -.02 | .13* | -.12* | -.02 | .04 | .12 | -.12 |
| **PCR.L** | -.04 | -.04 | -.05 | .04 | -.12 | .02 | .02 |
| **PCR.R** | -.02 | .01 | -.04 | -.04 | -.06 | .01 | .06 |
| **PLIC.L** | .00 | -.03 | .05 | -.08 | .05 | .14 | -.09 |
| **PLIC.R** | -.01 | .00 | .02 | -.07 | .02 | .10 | -.04 |
| **PTR.L** | .00 | .01 | -.12* | .13 | .12 | .09 | -.02 |
| **PTR.R** | .02 | .05 | -.05 | .08 | .08 | .05 | .02 |
| **RLIC.L** | -.03 | -.04 | -.01 | -.06 | -.02 | -.01 | .00 |
| **RLIC.R** | -.04 | .06 | -.11* | -.09 | .02 | .02 | -.11 |
| **SCR.L** | -.01 | -.03 | -.03 | .02 | .09 | .10 | -.01 |
| **SCR.R** | -.02 | .01 | -.04 | -.04 | .07 | .13 | -.03 |
| **SFO.L** | .01 | .03 | -.01 | .01 | .09 | .14 | -.08 |
| **SFO.R** | .01 | .05 | -.02 | .04 | .17* | .13 | -.12 |
| **SLF.L** | .02 | -.01 | .03 | .06 | .16 | .00 | -.02 |
| **SLF.R** | .06* | .00 | .09 | .03 | .24** | .13 | -.02 |
| **SS.L** | -.03 | -.10* | -.05 | .10 | .15 | .04 | .00 |
| **SS.R** | -.05 | .02 | -.17** | -.01 | .08 | .07 | -.06 |
| **TAP.L** | -.04 | -.08 | -.15* | .02 | .02 | -.04 | .16* |
| **TAP.R** | -.01 | .01 | -.05 | -.11 | -.06 | .01 | .14* |
| **UNC.L** | .00 | -.06 | .04 | .08 | .11 | -.09 | .00 |
| **UNC.R** | .00 | .00 | -.05 | .12 | .21* | .09 | -.07 |

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**Supplementary Table 15. Relationship between AD and disease duration by syndrome**. Partial correlations between AD in each ROI and disease duration controlling for age, age$^2$ and sex. Results are split by syndrome: all syndromes (All), temporal lobe epilepsy with hippocampal sclerosis in the left and right hemisphere (TLE-HS-l and TLE-HS-r respectively), non-lesional temporal lobe epilepsy in the left and right hemisphere (TLE-NL-l and TLE-NL-r respectively), genetic generalized epilepsy (GGE) and extra temporal (Extra). ROIs are separated by left (.L) and right (.R) hemisphere where indicated. Significance was set at *** $p$ =< 0.001 (controlling for multiple comparisons, one sided). * $p < 0.05$ ** $p < 0.01$ *** $p$ =< 0.001.

| ROI | All | TLE-HS-l | TLE-HS-r | TLE-NL-l | TLE-NL-r | GGE | ExE |
|---|---|---|---|---|---|---|---|
| **AverageAD** | .03 | -.02 | .12* | -.04 | -.13 | -.06 | .02 |
| **BCC** | -.01 | -.04 | -.04 | -.01 | -.06 | -.01 | .01 |
| **GCC** | .02 | .06 | -.03 | -.06 | -.16 | -.09 | .06 |
| **SCC** | .05 | .03 | .09 | -.03 | .00 | .08 | -.08 |
| **ACR.L** | .03 | .04 | .06 | -.08 | -.08 | -.07 | .03 |
| **ACR.R** | .04 | .02 | .11 | -.09 | -.16 | -.10 | .12 |
| **ALIC.L** | -.01 | .01 | -.10 | -.01 | -.12 | .03 | .11 |
| **ALIC.R** | -.02 | .02 | -.13* | -.08 | -.22* | -.03 | .19* |
| **CGC.L** | -.06* | -.07 | -.05 | -.04 | -.07 | .09 | .02 |
| **CGC.R** | -.04 | -.10 | -.03 | .01 | -.14 | .03 | .14* |
| **CGH.L** | -.03 | -.05 | .02 | -.06 | -.10 | -.10 | .01 |
| **CGH.R** | .00 | -.04 | .11 | -.04 | -.10 | -.03 | .02 |
| **CST.L** | -.02 | -.08 | .14* | -.04 | -.19* | -.01 | .00 |
| **CST.R** | -.04 | -.09 | .07 | -.13 | -.22* | .01 | .02 |
| **EC.L** | -.01 | -.02 | -.05 | -.01 | -.14 | -.04 | .10 |
| **EC.R** | -.03 | -.08 | -.07 | -.04 | -.18* | -.07 | .19** |
| **FX.ST.L** | .01 | -.04 | .09 | .08 | -.07 | -.07 | -.04 |
| **FX.ST.R** | .01 | -.13* | .10 | -.02 | .01 | -.14 | .09 |
| **PCR.L** | .05 | .05 | .10 | -.06 | -.04 | -.03 | .00 |
| **PCR.R** | .03 | .00 | .06 | .08 | -.02 | -.03 | -.05 |
| **PLIC.L** | .00 | .01 | -.09 | .13 | -.04 | -.14 | .10 |
| **PLIC.R** | .01 | .02 | -.07 | .08 | -.01 | -.12 | .07 |
| **PTR.L** | .00 | -.02 | .09 | -.11 | -.20* | -.08 | .04 |
| **PTR.R** | -.03 | -.06 | .04 | -.08 | -.16 | -.05 | -.04 |
| **RLIC.L** | .04 | .01 | .02 | .09 | .04 | .02 | .05 |
| **RLIC.R** | .04 | -.08 | .10 | .11 | -.03 | -.02 | .16* |
| **SCR.L** | .00 | -.01 | .01 | .02 | -.11 | -.10 | .04 |
| **SCR.R** | .01 | -.01 | .02 | .02 | -.03 | -.14 | .06 |
| **SFO.L** | -.04 | -.07 | -.05 | -.07 | -.01 | -.14 | .08 |
| **SFO.R** | -.03 | -.04 | -.05 | -.12 | -.12 | -.13 | .16* |
| **SLF.L** | -.02 | -.01 | -.02 | -.05 | -.06 | -.01 | .04 |
| **SLF.R** | -.06* | -.03 | -.08 | -.05 | -.17 | -.15 | .06 |
| **SS.L** | .03 | .08 | .04 | -.09 | -.08 | -.05 | .05 |
| **SS.R** | .04 | -.02 | .14* | -.09 | -.06 | -.08 | .11 |
| **TAP.L** | .05 | .09 | .19** | -.05 | -.11 | .04 | -.11 |
| **TAP.R** | -.02 | -.03 | .05 | .05 | -.16 | -.02 | -.14* |
| **UNC.L** | -.01 | .03 | -.06 | -.12 | -.05 | .08 | -.01 |
| **UNC.R** | -.02 | -.06 | .02 | -.08 | -.13 | -.10 | .06 |

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**Supplementary Table 16. Follow-up premutation testing of FA differences between controls and epilepsy patients.** To check that heteroscedasticity was not influencing results, FSL PALM was used to test if permutation testing of the difference in FA between patients and controls was similar to the core ANCOVA results (Fig. 3, Supplementary Table 4). The simulated significance P(sim) threshold was set at $p < 0.001$.

| ROI | *v* | *P(sim)* |
|---|---|---|
| **AverageFA** | 12.0497 | 0.0001 |
| **BCC** | 12.2958 | 0.0001 |
| **GCC** | 10.1637 | 0.0001 |
| **SCC** | 5.7422 | 0.0001 |
| **ACR-L** | 9.3719 | 0.0001 |
| **ACR-R** | 9.6532 | 0.0001 |
| **ALIC-L** | 8.1954 | 0.0001 |
| **ALIC-R** | 6.9274 | 0.0001 |
| **CGC-L** | 10.9109 | 0.0001 |
| **CGC-R** | 9.9744 | 0.0001 |
| **CGH-L** | 9.9126 | 0.0001 |
| **CGH-R** | 9.3407 | 0.0001 |
| **CST-L** | 3.4363 | 0.0252 |
| **CST-R** | 3.3421 | 0.0401 |
| **EC-L** | 12.3362 | 0.0001 |
| **EC-R** | 12.4861 | 0.0001 |
| **FX/ST-L** | 8.5085 | 0.0001 |
| **FX/ST-R** | 9.0563 | 0.0001 |
| **PCR-L** | 7.4915 | 0.0001 |
| **PCR-R** | 8.3506 | 0.0001 |
| **PLIC-L** | 4.1092 | 0.0002 |
| **PLIC-R** | 5.4984 | 0.0001 |
| **PTR-L** | 7.8169 | 0.0001 |
| **PTR-R** | 7.4353 | 0.0001 |
| **RLIC-L** | 7.2476 | 0.0001 |
| **RLIC-R** | 7.0187 | 0.0001 |
| **SCR-L** | 6.378 | 0.0001 |
| **SCR-R** | 6.3812 | 0.0001 |
| **SFO-L** | 6.0982 | 0.0001 |
| **SFO-R** | 5.0347 | 0.0001 |
| **SLF-L** | 9.0426 | 0.0001 |
| **SLF-R** | 9.9794 | 0.0001 |
| **SS-L** | 11.1949 | 0.0001 |
| **SS-R** | 11.264 | 0.0001 |
| **TAP-L** | 8.3146 | 0.0001 |
| **TAP-R** | 7.2814 | 0.0001 |
| **UNC-L** | 6.8515 | 0.0001 |
| **UNC-R** | 10.1114 | 0.0001 |

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