Shared genetic underpinnings between genetic generalized epilepsy and background EEG oscillations

Running head: Genetic overlap between epilepsy and EEG

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Abstract

Objective:

Paroxysmal epileptiform abnormalities on electroencephalography (EEG) are the hallmark of epilepsies, but it is uncertain to what extent epilepsy and background EEG oscillations share neurobiological underpinnings. Here, we aimed to assess the genetic correlation between epilepsy and background EEG oscillations.

Methods:

Confounding factors, including the heterogeneous etiology of epilepsies and medication effects hamper studies on background brain activity in people with epilepsy. To overcome this limitation, we compared genetic data from a GWAS on epilepsy (n=12,803 people with epilepsy and 24,218 controls) with that from a GWAS on background EEG (n=8,425 subjects without epilepsy), in which background EEG oscillation power was quantified in four different frequency bands: alpha, beta, delta and theta. We replicated our findings in an independent epilepsy replication dataset (n=4851 people with epilepsy and 20,428 controls). To assess the genetic overlap between these phenotypes, we performed genetic correlation analyses using linkage disequilibrium score regression, polygenic risk scores and Mendelian randomization analyses.

Results:

Our analyses show strong genetic correlations between genetic generalized epilepsy (GGE) with background EEG oscillations, primarily with the beta frequency band. Furthermore, we show that subjects with higher beta and theta polygenic risk scores have a significantly higher risk of having generalized epilepsy. Mendelian randomization analyses suggest a causal effect of GGE genetic liability on beta oscillations.

Significance:

Our results point to shared biological mechanisms underlying background EEG oscillations and the susceptibility for GGE, opening avenues to investigate the clinical utility of background EEG oscillations in the diagnostic work-up of epilepsy.

Keywords: GGE, generalized epilepsy, EEG, oscillations, beta-power, PRS.

Introduction

The power of oscillations in background EEG is a highly stable and heritable human trait [1]. It is easily acquired and can be automatically analyzed by software, rather than subjective interpretation. Epilepsy is highly heritable and is characterized by altered brain excitability [2,3]. Oscillatory activity is believed to serve an essential role in cortico-thalamic functioning, and can be measured as power of oscillations in background EEG at different broad-band frequencies [4]. Neurophysiological relationships between background EEG and generalized epileptiform discharges have been well described [5-8]. However, it is currently unknown whether background oscillatory activity is itself associated with epilepsy, and whether background EEG and epilepsy have a shared neurobiological and genetic basis.

There have been some studies where background EEG oscillations measurements have been directly compared between people with epilepsy and healthy controls. However, such studies have yielded conflicting results, most likely because sample sizes were small and anti-seizure drugs can strongly affect EEG measurements [11-16]. These limitations and bias can be overcome by large-scale genetic studies, in which genetic determinants of background EEG measurements are assessed independently in healthy controls (presumably not taking anti-seizure drugs). These genetic determinants can than be compared to genetic determinants of different epilepsy phenotypes, as assessed in a different study. Comparing these independent studies allows for a well-powered and unbiased assessment of shared genetic determinants of epilepsy and EEG oscillations.

Here, we therefore assessed whether oscillatory background EEG is genetically correlated with focal and generalized epilepsy. The association between genetic variants and background brain activity was previously investigated in a genome-wide association study (GWAS) on 8,425 subjects without epilepsy [9]. We combined this data with our recently published large GWAS of epilepsy [10], to examine genetic correlations between several types

of epilepsy and oscillatory brain activity across frequency bands (delta: 1-3.75Hz, theta: 4-7.75 Hz, alpha: 12.75 Hz and beta: 13-30Hz). Next, we utilized polygenic risk scoring (PRS) to assess whether patients with GGE have a genetic predisposition towards altered background brain activity. We then replicated genetic correlation and polygenic analyses using an independent cohort from the Epi25 Collaborative (n=4,851 people with epilepsy and 20,428 controls). Finally, we performed Mendelian Randomization to gain insight into possible causal relationships between genetic variants associated with epilepsy and those associated with background EEG. We thus provide converging evidence for consistent cross-trait genetic overlap between epilepsy and background EEG.

Methods

Study population: discovery dataset

The participants derived from the epilepsy GWASs [10] for the current analyses were Caucasian subjects. The epilepsy GWAS included 13 control cohorts [10]. Case/control ascertainment and diagnostic criteria were previously reported [10]. As described previously [10], epilepsy specialists diagnosed patients and ascertained phenotypic subtypes. Population-based datasets, some of which had been screened to exclude neurological disorders, were used as controls. However, due to the relatively low prevalence of epilepsy in the general population (~0.5-1%), screening to exclude epilepsy in control cohorts it will only have a minor effect on statistical power. Summary statistics from the recent epilepsy GWAS conducted by the ILAE Consortium on Complex Epilepsies GWAS were available for n=12,803 cases (suffering from either focal or generalized epilepsy) and 24,218 controls [10]. From those participants the following subjects were excluded for those analyses requiring individual-level genotype data: Finnish ancestry (none had GGE) and the subset of the EPICURE-SP1 cohort that lacked informed consent for the current analyses, resulting in subject-level genotype data being

available for 11,446 patients with epilepsy and 22,078 controls. Subjects with epilepsy were stratified into GGE (n=3,122) and focal epilepsy (n=8,324); GGE was further subdivided into childhood absence epilepsy (CAE; n=561), juvenile absence epilepsy (JAE; n=311), juvenile myoclonic epilepsy (JME; n=1,000) and generalized tonic-clonic seizures only (GTCS only; n=195). GGE subtype information was not available for 1055 patients.

We downloaded summary statistics of the ENIGMA-EEG GWAS of resting state oscillation power in the delta (1-3 Hz), theta (4-8 Hz), alpha (8-12 Hz), and beta (13-30 Hz) bands at the vertex (Cz) electrode (n=8,425 participants) [9]. This EEG GWAS study was based on 5 cohorts from 4 cooperating centers. Although the selection criteria varied across cohorts, all adult cohorts included epilepsy and prolonged unconsciousness after head trauma as exclusion criteria which were communicated at the time of recruitment or at the first lab visit; since neurological disorders were an exclusion criterium, we do not expect subjects to be taking anti-seizure drugs (although this was no explicit exclusion criterium). All these were self or parent-reported retrospective questions. A fuller sample description is presented in the original study [9].

Approval for the source studies was obtained by all relevant institutional review boards and all study participants provided written informed consent according to the Declaration of Helsinki.

Replication dataset

To replicate our findings, we used data from the Epi25 collaborative (http://epi-25.org/). This cohort currently constitutes 4,851 people with epilepsy, of whom 2,612 have focal epilepsy and 2,239 have GGE (no data on GGE subtypes were available). The cases were matched to a total of 20,428 controls from the Partners Healthcare Biobank (n=14,857), the Epi25 collaborative (n=210), the Genetics and Personality consortium (n=456), and an in-house

project on inflammatory bowel disease (n=4,905). The cohorts were genotyped on the Illumina Global Screening Array, with the exception of the Partners Healthcare Biobank participants, who were genotyped on the Illumina Multi-Ethnic Screening Array. Approval was obtained by all relevant institutional review boards and all study participants provided written informed consent according to the Declaration of Helsinki.

Genetic correlation analyses

Genetic correlations between epilepsy subtypes and oscillatory brain activity were computed using bivariate linkage-disequilibrium score regression (LDSC) [22]. For these analyses, as no individual-level genotype data were available from the EEG dataset, we used published summary statistics of the EEG frequency bands (alpha, beta, delta and theta; n=8,425 participants) and the epilepsy subtypes (focal, GGE, CAE, JAE, JME and GTCS only; n=12,803 cases suffering from either focal or generalized epilepsy and 24,218 controls) from the ILAE consortium as a discovery dataset [10]. For LDSC replication analyses, we used unpublished data from the Epi25 collaborative (http://epi-25.org/; n=4,851 people with epilepsy and 20,428 controls). For discovery and replication LDSC analyses, default settings of LDSC were used, with pre-computed LD score weights derived from the European subset of the 1000 Genomes project [23]. See Supplemental Table 1 for the numbers of SNPs per LDSC analysis. The significance threshold was Bonferroni-corrected for the two main epilepsy subtypes studied (GGE and focal) but not for the EEG power spectra, since these were all highly correlated at $p<10^{-17}$ (Supplemental Table 2), resulting in a significance threshold of p=0.05/2=0.025. Similarly, we did not correct for the individual GGE subtypes, which are phenotypically similar and genetically highly correlated [10].

Polygenic risk score analyses

For PRS analyses we used individual-level genotype data derived from the epilepsy GWAS [10] and summary statistics from the EEG GWAS [9]. Quality control was performed as reported in the published epilepsy GWAS [10]. We then added a genotype filter for call rate >0.99 and the exclusion of genetically related subjects to allow for highly conservative PRS estimates. Genetic inter-relatedness was calculated with KING [24] and one subject from each pair with third-degree or higher relatedness (kinship coefficient >0.0442) was excluded. PRSice [25] was used with default settings to assess whether subjects with epilepsy have different EEG frequency power PRSs compared to controls. In brief, to each SNP we assigned a weight proportional to its association in the four EEG GWASs (alpha, beta, delta and theta). Next, individual PRSs were calculated as the sum of weighted effect alleles for every subject from the epilepsy cohort. These PRSs were standardized with a Z-score transformation: $\frac{PRS-mean(PRS)}{SD(PRS)}$. SNPs were pruned to a subset of genetically uncorrelated SNPs (linkage disequilibrium R^2<0.1) and PRS values were calculated using a number of different P-value thresholds (P_ts) from 0.0001 to 0.5. Next, logistic regression analyses, corrected for sex and 10 genetic ancestry principal components, were performed to assess the association of these PRS scores with GGE. The PRSs with the highest association with GGE was chosen as the 'best-fit', after which logistic regression analyses were repeated to assess the association of this PRS with the other epilepsy subtypes. We used a conservative p<0.001 significance threshold to correct for multiple comparisons, as recommended for PRSice [25]. Δ Explained variance represented by the Nagelkerke R^2 was computed using a logistic regression of the PRS, subtracted by the baseline model (covariates only: sex and 4 PCs). To quantify the association of beta-power PRS with GGE, we used PRSice standard settings to divide subjects into 10 deciles based on their beta-power PRS scores. We then performed logistic regression to compare the risk of having GGE between every decile with the lowest

(0-10%) as a reference (corrected for sec and 4 PCs). We then repeated the analyses in the independent Epi25 cohort. This dataset contained approximately one-third fewer GGE cases than the discovery cohort, providing insufficient power to exactly replicate our discovery PRS findings. We therefore performed quasi-replication using a one-sample test of the proportion to assess concordance effect directions between discovery and replication PRS analyses, computing z-scores that were converted into p-values:

$$z = \frac{\hat{p} - p_0}{\sqrt{p_0(1 - p_0)/n}}$$

where the p = the sample proportion; H_0 represents the null hypothesis: $p = p_0$; and the alternative hypothesis H_1: $p \neq p_0$.

Mendelian Randomization

To explore possible causal effects of GGE genome-wide loci on EEG background oscillations, we conducted Mendelian Randomization analyses using GGE and EEGs summary statistics data. 228 SNPs significantly associated with GGE ($p<5x10^{-8}$) were extracted from both the GGE and EEG GWASs. The summary statistics of 228 SNPs were harmonized to ensure the SNP effect direction corresponded with equal effect alleles across GGE and EEG. We used the "TwosampleMR" package [29] in R to perform fixed effects inverse variance-weighted (IVW), weighted median, and MR Egger models. We then performed sensitivity analyses, including horizontal pleiotropic effects estimated by the intercept of MR Egger, residual heterogeneity due to pleiotropy estimated by Cochran's Q test [30], and leave-one-out analyses (for the IVW-fixed effect model) to evaluate if any single instrumental variable was driving the results. GSMR (generalized summary-data based mendelian randomisation) analyses were performed using the "GSMR" [31] package in R. To

that end, first the LD matrix of the selected SNPs was calculated using PLINK [32] and GCTA [33] within 1000 Genomes Phase 3 data [23]. The minimum number of instrumental variables in the GSMR model was loosened from 10 to 5 as there were only 8 independent (r^2<0.01, LD window =10Mb) significant loci identified in the GWAS of GGE (and none in the EEG GWAS). We used default options in GSMR with Heterogeneity in Dependent Instruments (HEIDI) testing for instrumental outliers' detection. At the end, we repeated GSMR with loosened LD prune thresholds (namely r2<0.1, r2<0.15 and r2<0.2) because GSMR takes LD structure into account by adding the LD matrix. The significance threshold was Bonferroni corrected for all these seven mendelian randomisation models (p=0.05/7=0.007).

Data availability

GWASs summary statistics used for the current analyses are available online: http://enigma.ini.usc.edu/research/download-enigma-gwas-results/; http://www.epigad.org/gwas_ilae2018_16loci.html.

Results

Genetic correlations between epilepsy and oscillatory brain activity

In a total study population of 45,446 subjects (n=8,425 from the EEG and n=37,021 from the epilepsy GWASs), we computed genetic correlations between alpha, beta, delta and theta oscillatory brain activity with focal epilepsy and GGE. We found significant correlations between GGE and beta-power (Rg=0.44 ± s.e. of 0.18; p=0.01) and theta-power (Rg=0.25 ± 0.11; p=0.02; **Figure 1**, upper panel, Supplemental table 1). This was further supported by the correlations between beta and theta-power with the GGE subtypes CAE, JAE and JME: all had similarly high correlation coefficients. We found no genetic correlations between focal epilepsy and any of the EEG phenotypes. We then attempted to replicate the genetic

correlations using the unpublished Epi25 dataset and found similar genetic correlations (both in sign and effect size) to the discovery analyses (**Figure 1**, lower panel): GGE correlated with beta power (Rg=0.52 ± 0.21, p=0.01), while the genetic correlation between theta power and GGE paralleled the discovery cohort (albeit not reaching significance: Rg=0.16 ± 0.12; p=0.18). All genetic correlation estimates with focal epilepsy were again non-significant. There was no data was available for GGE subtypes.

Oscillatory brain activity polygenic scores are associated with generalized epilepsy

We used polygenic scoring to utilize the full distribution of background EEG associated SNPs to assess whether people with epilepsy have a different polygenic score for specific frequency bands compared to controls. We observed significant positive associations between beta and theta-power PRSs with GGE, in line with the LDSC results (**Figure 2)**. In particular beta power PRSs were strongly associated with GGE (beta=0.11; s.e.= 0.020; $p=5.3x10^{-8}$; explained variance 0.21%; **Figure 2**), which was further supported by significant associations of beta power PRS with its subtypes CAE (beta=0.15; s.e.=0.044; $p=8.5x10^{-4}$) and JME (beta=0.12; s.e.=0.033; $p=3.6x10^{-4}$). Furthermore, of the participants in the GGE case-control cohort, those in the highest 10% decile of beta-power PRS scores were 1.4 fold more likely to have GGE compared to the people in the lowest 10% PRS decile (Supplemental Figure 1; OR: 1.40; 95%CI: 1.18-1.67; $p=1.5x10^{-4}$). When using the independent Epi25 cohort as a replication dataset we found that the directions of effect agreed with the discovery analyses for all associations between EEG PRSs and GGE ($p_{one\text{-}sided}$= 0.023; $p_{two\text{-}sided}$= 0.046; supplemental Figure 2). EEG PRSs were not significantly different between people with focal epilepsy and controls.

Mendelian Randomization analyses

Mendelian randomisation (MR) analyses were performed to assess potential causative relationships between background EEG and GGE. Eight GGE-associated SNPs were selected as instrumental variables at a strict LD prune threshold (r^2<0.01, LD window =10Mb). These were used in fixed effects IVW, weighted median, MR Egger, and GSMR (r^2<0.01) models. After loosening the LD threshold, 11 (r^2<0.1), 12 (r^2<0.15) and 14 (r^2<0.2) SNPs were selected as instrumental variables for GSMR models. Causal effects of GGE loci on beta oscillations were found at the LD r^2< 0.15 and <0.2 thresholds (OR=1.79, CI=1.189-2.707, P-value= $5.2x10^{-3}$; and OR=1.723, CI=1.180-2.516, P-value=$4.8x10^{-3}$, respectively, **Figure 4**, Supplemental Table 4, Supplemental Figure 3). Significant heterogeneity was detected in the fixed-effect IVW model (Q-statistics=18.188, df=7, p= 0.01) and MR Egger model (Q-statistics=14.594, df=6, p= 0.02). No SNPs altered the pooled β coefficient in the leave-one-out sensitivity analysis (β =0.374, p= 0.314) in the fixed-effect IVW model. We found no evidence of horizontal pleiotropic effects. Similarly, the HEIDI test detected no SNPs as pleiotropic outliers.

Discussion

Here we leveraged the largest currently available GWASs to assess shared genetic underpinnings of epilepsy and of background EEG oscillations. In particular, we found strong genetic relationships between GGE and beta-power osccillations, which were replicated in an independent sample.

Previous studies comparing EEG background oscillations between epilepsy patients and controls are inconsistent: some show increased power in all frequency bands (alpha, beta, delta, theta), whereas others show only increases in specific frequency bands or even decreases in power [11-16]. This heterogeneity likely reflects multiple variables that are difficult to control for in clinical studies, such as AED usage, sleep deprivation, influence of (inter-)

ictal epileptic brain activity, EEG processing and electrode placement. We overcame such limitations by determining the genetic underpinnings of EEG frequency bands in people without epilepsy who are AED-naïve, and with a consistent electrode placement and signal processing. We applied several statistical models to assess this overlap and found that people with generalized, but not focal, epilepsy carry a relative abundance of genetic variation associated with higher beta oscillations. Mendelian Randomisation analyses pointed to causal effects of genetic liability to GGE on beta power.

We did not find genetic correlations between background EEG and focal epilepsy. Although power was limited for this analysis, this finding is consistent with the low contribution of common genetic variants in focal epilepsy and the lack of genetic overlap between focal and generalized epilepsy[10]. Focal epilepsy is likely to represent a more heterogenous group of different causes of epilepsy, many of which do not have a primary genetic cause (e.g. symptomatic epilepsy after traumatic brain injury). Moreover, focal epilepsy by definition only affects one part of the brain, and is therefore less likely to be associated by germline genetic variation and background EEG oscillations which most likely affect the whole brain. In contrast to focal epilepsy, the EEG discharges that characterize generalized epilepsy are dependent on the thalomocortical system [5,17]. Similarly, background oscillations have been functionally attributed to the thalamocortical system [18,19], suggesting that thalamocortical functioning could represent a common neurobiological mechanisms reflecting overall brain excitability which influences both GGE risk and (beta-power) background oscillations.

Our results should be interpreted in light of several limitations. First, we are aware of the possible advantages of using Genome Complex Trait Analysis (GCTA) relative to LDSC but since no subject-level genotype data are available for the EEG GWAS, we restricted our genetic correlation estimates LDSC, which is based on summary statistics. LDSC has proven

to be a reliable method for genetic correlation estimates and results between LDSC and GCTA have proven consistent. Second, we found that the same genetic variants underlie both GGE and beta-power oscillations, but our study does not prove that people with GGE indeed have altered background oscillations, since we did not have EEG measurements of people with epilepsy in this study. Third, only one-way Mendelian Randomisation analyses were performed due to lack of genome-wide significant loci in the EEG GWAS. We therefore cannot exclude the possibility of bidirectional causality between EEG and GGE. Fourth, we had insufficient data available to carry out subgroup analyses on subjects with non-lesional focal epilepsy patients.

Altogether, our results point to shared biological mechanisms underlying background EEG oscillations and the susceptibility for generalized seizures. Our findings thus open avenues to investigate the clinical utility of background oscillations in genetic generalized epilepsy. Potentially, prospective studies could confirm whether altered beta-oscillatons could be a prodromal state of GGE or whether aberrant beta oscillations constitute a feature of epilepsy. Future studies may also integrate transcranial magnetic stimulation – EEG (TMS-EEG) and/or event-related potentials to examine whether beta and theta powers correlate with altered brain excitability in subjects with high epilepsy liability. Furthermore, machine-learning studies integrating background EEG with other sources of clinical and demographic data may one day increase diagnostic accuracy of epilepsy.

Key points box

- 1: Genetic correlation studies show shared genetic underpinnings between GGE and power of background oscillations in the beta-frequency band.
- 2: Polygenic risk score analyses show that subjects with more beta-power associated genetic variants have an increased risk of having GGE.

- 3: Mendelian randomization analyses suggest a causal relationship of GGE genetic liability on beta oscillations.

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Disclosure of Conflicts of interest

None of the authors has any conflict of interest to disclose.

Author contributions statement

RS, JJL, DS and BPCK contributed to the conception and design of the study.

RS, JJL, BDL, DS and BPCK contributed to the acquisition and analysis of data.

RS, JJL, BDL, CL, DL, AS, DS, JAC, KR, RARB, KPJB, FEJ, DS and BPJK contributed to the drafting of the manuscript and preparing the figures. Members of the ILAE consortium on Complex Epilepsies and EPI25 Collaborative contributed clinical and genetic data.

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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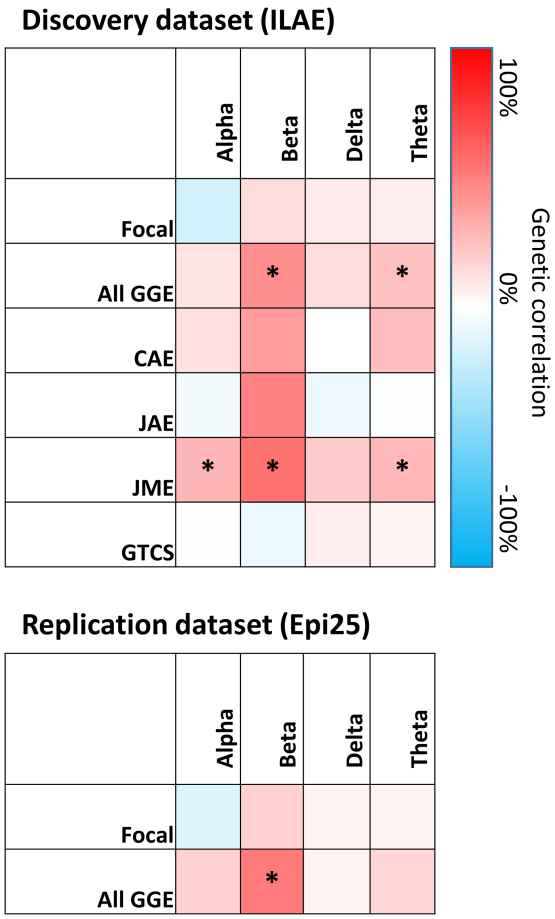
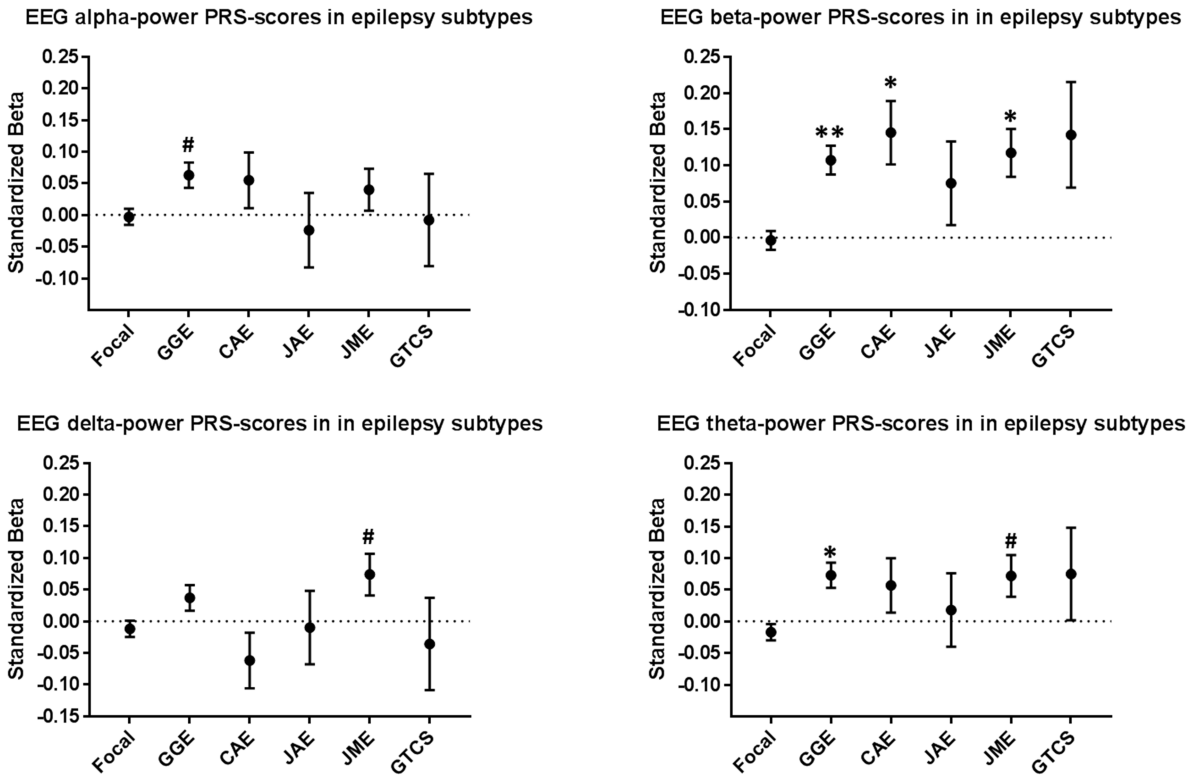
Figure legends

Figure 1: Genetic correlations between EEG frequency bands and epilepsy subtypes. Genetic correlations were calculated by comparing the EEG frequency band GWAS with the ILAE GWAS (upper panel, discovery dataset) and the Epi25 GWAS (lower panel, replication dataset). * $P<0.05$.

Figure 2 A: Beta and theta power EEG oscillation polygenic risk scores (PRSs) are associated with generalized epilepsy but not with focal epilepsy. The 'best-fit' P-value threshold (P_t) was chosen based on the most significant association with GGE, which was then applied to all other epilepsy subtypes. The number of SNPs included in each model were: 2,670 for Alpha power (P_t =0.0105), 10,861 for Beta power (P_t=0.06245), 8,182 for Delta power (P_t =0.0446), and 3,833 for Theta power (P_t=0.01665). Logistic regression analyses were performed to assess the association between the PRSs and the different epilepsy subtypes, corrected for sex and 10 principal components. #: $P<0.05$; *: $P<0.001$; **: $P<10^{-7}$. Focal = focal epilepsy; GGE = genetic generalized epilepsy; CAE (childhood absence epilepsy), JAE (juvenile absence epilepsy), JME (juvenile myoclonic epilepsy) and GTCS (generalized tonic-clonic seizures only) are GGE subtypes.

Figure 3. Scatter plot of instrumental SNPs associated with generalized epilepsy tested for EEG beta oscillations. The instrumental variables passed Heterogeneity in Dependent Instruments (HEIDI) testing for instrumental outliers from GSMR detection with multiple LD prune thresholds. Lines in red, yellow, light green and dark green represent β for fixed effect IVW, weighted median, MR Egger, and GSMR models using 8 instruments ($r^2<0.01$). The lines in blue purple and pink represent βs from GSMR model with 11 ($r^2<0.1$), 12 ($r^2<0.15$) and 14 ($r^2<0.2$) instruments in GSMR.


Discovery dataset (ILAE)
Alpha
Beta
Delta
Theta
Focal
All GGE
CAE
JAE
JME
GTCS
*
*
*
*
*
100%
0%
-100%
Genetic correlation
Replication dataset (Epi25)
Alpha
Beta
Delta
Theta
Focal
All GGE
*


EEG alpha-power PRS-scores in epilepsy subtypes
Standardized Beta
0.25
0.20
0.15
0.10
0.05
0.00
-0.05
-0.10
#
Focal
GGE
CAE
JAE
JME
GTCS
EEG beta-power PRS-scores in in epilepsy subtypes
Standardized Beta
0.25
0.20
0.15
0.10
0.05
0.00
-0.05
-0.10
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*
Focal
GGE
CAE
JAE
JME
GTCS
EEG delta-power PRS-scores in in epilepsy subtypes
Standardized Beta
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0.05
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-0.15
#
Focal
GGE
CAE
JAE
JME
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EEG theta-power PRS-scores in in epilepsy subtypes
Standardized Beta
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0.20
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0.00
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Focal
GGE
CAE
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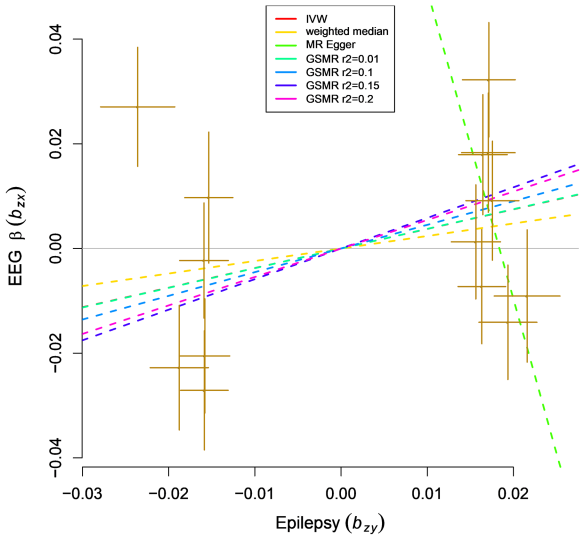
GTCS


IVW
weighted median
MR Egger
GSMR r2=0.01
GSMR r2=0.1
GSMR r2=0.15
GSMR r2=0.2
EEG β (b_{zx})
Epilepsy (b_{zy})
0.04
0.02
0.00
−0.02
−0.04
−0.03
−0.02
−0.01
0.00
0.01
0.02