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Authors

Karadag, Naz

Hagen, Espen

Shadrin, Alexey

et al.

Publication Date

2024-11-01

DOI

10.1016/j.seizure.2024.09.016

Peer reviewed

HHS Public Access

Author manuscript

Seizure. Author manuscript; available in PMC 2024 December 28.

Published in final edited form as:

Seizure. 2024 November ; 122: 105–112. doi:10.1016/j.seizure.2024.09.016.

Unraveling the shared genetics of common epilepsies and general cognitive ability

Naz Karadag, MSc[1,#], **Espen Hagen, PhD**[1,#], **Alexey A. Shadrin, PhD**[1,2], **Dennis van der Meer, PhD**[1,3], **Kevin S. O'Connell, PhD**[1], **Zillur Rahman, PhD**[1], **Gleda Kutrolli, PhD**[1], **Nadine Parker, PhD**[1], **Shahram Bahrami, PhD**[1], **Vera Fominykh, MD, PhD**[1], **Kjell Heuser, MD, PhD**[4], **Erik Taubøll, MD, PhD**[4,5], **Torill Ueland, PhD**[6,7], **Nils Eiel Steen, MD, PhD**[1,6,8], **Srdjan Djurovic, PhD**[9,10], **Anders M. Dale, PhD**[11,12,13,14], **Oleksandr Frei, PhD**[1,15], **Ole A. Andreassen, MD, PhD**[1,2,6], **Olav B. Smeland, MD, PhD**[1,6]

[1]Centre for Precision Psychiatry, Division of Mental Health and Addiction, University of Oslo and Oslo University Hospital Oslo, Norway

[2]K.G. Jebsen Centre for Neurodevelopmental disorders, University of Oslo and Oslo University Hospital, Oslo, Norway

[3]School of Mental Health and Neuroscience, Faculty of Health, Maastricht University, Maastricht, Netherlands

[4]Department of Neurology, Oslo University Hospital, Oslo, Norway

[5]Faculty of Medicine, University of Oslo, Oslo, Norway

[6]Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway

[7]Department of Psychology, University of Oslo, Oslo, Norway

[8]Department of Psychiatric Research, Diakonhjemmet Hospital, Oslo, Norway

[9]Department of Medical Genetics, Oslo University Hospital, Oslo, Norway

[10]Department of Clinical Science, University of Bergen, Bergen, Norway

Corresponding Author: Naz Karadag, MSc, Centre for Precision Psychiatry, Division of Mental Health and Addiction, University of Oslo and Oslo University Hospital, Kirkeveien 166, 0424 Oslo, Norway, naz.karadag@medisin.uio.no.

[#]Shared first-author

Author Contributions

Conceived and designed the analysis: N.K., E.H., O.A.A., O.B.S.; Contributed data or analysis tools: E.H., A.A.S., Z.R., G.K., N.P., O.F., A.M.D., O.A.A. ; Performed the analysis: N.K., E.H., A.A.S., G.K., N.P.; Drafting the article: N.K., E.H., O.B.S.; Critical revision of the article: N.K., E.H., A.A.S., D.V.D.M., K.S.O., Z.R., G.K., N.P., S.B., V.F., K.H., E.T., T.U., N.E.S., S.D., A.M.D., O.F., O.A.A., O.B.S.; Final approval of the version to be published: N.K., E.H., A.A.S., D.V.D.M., K.S.O., Z.R., G.K., N.P., S.B., V.F., K.H., E.T., T.U., N.E.S., S.D., A.M.D., O.F., O.A.A., O.B.S.

Statement of Ethics

All GWAS investigated in the present study were approved by the local ethics committees, and informed consent was obtained from all participants. We thank the ILAE and 23andMe consortia and the FinnGen Biobank for access to data, and the many participants who provided DNA samples.

Disclosure of Conflicts of Interest

O.A.A. has received speaker's honorarium from Lundbeck, Sunovion, Takeda, Janssen and is a consultant for CorTechs.ai and Precision Health AS. A.M.D. is a founder of and holds equity interest in CorTechs Labs and serves on its scientific advisory board. He is also a member of the Scientific Advisory Board of Healthlytix and receives research funding from General Electric Healthcare (GEHC). The terms of these arrangements have been reviewed and approved by the University of California, San Diego in accordance with its conflict-of-interest policies. The remaining authors have no conflicts of interest to declare.

[11]Department of Cognitive Science, University of California, San Diego, United States

[12]Multimodal Imaging Laboratory, University of California, San Diego, United States

[13]Department of Psychiatry, University of California, San Diego, United States

[14]Department of Neurosciences, University of California, San Diego, United States

[15]Center for Bioinformatics, Department of Informatics, University of Oslo, Oslo, Norway

Abstract

Purpose: Cognitive impairment is prevalent among individuals with epilepsy, and increasing evidence indicates that genetic factors can underlie this relationship. However, the extent to which epilepsy subtypes differ in their genetic relationship with cognitive function, and information about the specific genetic variants involved remain largely unknown.

Methods: We investigated the genetic relationship between epilepsies and general cognitive ability (COG) using complementary statistical tools, including linkage disequilibrium score (LDSC) regression, MiXeR and conjunctional false discovery rate (conjFDR). We analyzed genome-wide association study data on COG (n = 269,867) and common epilepsies (n = 27,559 cases, 42,436 controls), including the broad phenotypes ‘all epilepsy’, focal epilepsies and genetic generalized epilepsies (GGE), as well as specific subtypes. We functionally annotated the identified loci using several biological resources and validated the results in independent samples.

Results: Using MiXeR, COG (11.2k variants) was estimated to be almost four times more polygenic than ‘all epilepsy’, GGE, juvenile myoclonic epilepsy (JME), and childhood absence epilepsy (CAE) (2.5k – 2.9k variants). The other epilepsy phenotypes were insufficiently powered for MiXeR analysis. We quantified extensive genetic overlap between COG and epilepsy types, but with varying negative genetic correlations (−0.23 to −0.04). COG was estimated to share 2.9k variants with both GGE and ‘all epilepsy’, and 2.3k variants with both JME and CAE. Using conjFDR, we identified 66 distinct loci shared between COG and epilepsies, including novel associations for GGE (27), ‘all epilepsy’ (5), JME (5) and CAE (5). The implicated genes were significantly expressed in multiple brain regions. The results were validated in independent samples (COG: $p = 3.62 \times 10^{-7}$; ‘all epilepsy’: $p = 2.58 \times 10^{-3}$).

Conclusion: Our study further dissects the substantial genetic basis shared between epilepsies and COG and identifies novel shared loci. An improved understanding of the genetic relationship between epilepsies and COG may lead to the development of novel comorbidity-targeted epilepsy treatments.

Keywords

Epilepsy; Cognition; Polygenic Overlap; Linkage Disequilibrium Score Regression; LDSC; Gaussian Causal Mixture Models; MiXeR; Conjunctional False Discovery Rate; ConjFDR

1. Introduction

Epilepsies are diverse brain disorders characterized by unprovoked recurrent seizures [1]. Epilepsies contribute significantly to the global disease burden, affecting over 60 million

people worldwide of all ages [2]. The underlying pathogenesis remains poorly understood and many patients continue to suffer from uncontrolled seizures [3, 4]. Epilepsies are divided by seizure onset into two broad groups; focal epilepsies and generalized epilepsies, the latter being predominantly composed of genetic generalized epilepsies GGE. While focal epilepsies and GGE differ in their clinical presentations, both are associated with cognitive impairments, which substantially affect the quality of life of individuals with epilepsies [5, 6]. Cognitive impairments in individuals with epilepsies encompass difficulties with memory, attention, language and executive functioning, often predating seizure onset, emphasizing that cognitive impairment is not merely a consequence of seizures [5]. However, not all individuals with epilepsy have cognitive difficulties, with a wide range of cognitive performance among individuals with epilepsy suggesting a complex relationship between epilepsies and cognition [5, 7]. Moreover, cognitive ability is also variously associated with several clinical and etiological characteristics of epilepsy, including the origin, frequency and duration of seizures, age of seizure onset, duration of epilepsy, cerebral pathology, and effect of anti-seizure medication [8]. Further, studies have suggested that cognitive performance, particularly in the domains of intelligence and memory, has prognostic value for seizure outcomes in patients with epilepsies [9-11]. While surgical intervention may improve cognitive functioning in a selected group of focal epilepsy patients, anti-seizure medication is rather associated with a worsening of cognitive function by suppressing neuronal excitability or enhancing inhibitory neurotransmission [3, 12, 13]. Increasing evidence favors a bidirectional relationship between epilepsies and cognition, as part of pathogenesis, altering neural networks thereby leading to both cognitive impairments and seizure susceptibility [14, 15]. Enhancing our understanding of the potentially shared biology underlying epilepsies and cognition may help the development of novel comorbidity-targeted epilepsy treatments.

Both cognitive abilities and epilepsies are heritable [16-19]. Previous studies have estimated that the heritability attributable to common genetic variants is 19% for general cognitive ability COG and 9% and 32% for focal epilepsy and GGE, respectively [16, 19]. Recent genome-wide association studies GWAS have identified over 200 genomic loci associated with COG and over 60 loci associated with epilepsies [16-20]. Furthermore, significant negative genetic correlations between COG and epilepsies (‘all epilepsy’, focal epilepsies and GGE) have been reported (r_g = −0.20, −0.23, −0.14, respectively), suggesting that shared genetic underpinnings could contribute to cognitive impairment in epilepsies [16, 17, 21-23]. Moreover, recent modeling work using bivariate MiXeR[24] has estimated that a considerable fraction of the genetic architecture of GGE overlaps with COG [17]. However, to what extent other epilepsy subtypes share genetic variants with COG remains poorly understood and the specific loci jointly involved in these phenotypes are mostly unknown. Identifying these loci could expose the specific molecular genetic mechanisms shared between COG and epilepsies.

We here aimed to further dissect the shared common variant basis of epilepsies and COG leveraging recent large-scale GWAS and novel statistical tools. To this end, we analyzed GWAS datasets on COG and different epilepsy types, including the broad categories ‘all epilepsy’, focal epilepsies and GGE, as well as seven subtypes, using a set of complementary statistical tools: linkage disequilibrium score regression (LDSC) [25],

MiXeR [24] and conjunctional false discovery rate (conjFDR) [26, 27]. While LDSC [25] estimates pairwise global genetic correlations, MiXeR [24] estimates the number of variants underlying each phenotype as well as the number of variants shared between them, irrespective of the genetic correlations. Additionally, conjFDR improves the discovery of shared individual genomic loci between complex phenotypes [26, 27], which has been successfully applied to a wide range of traits and disorders in recent years [28, 29], including epilepsies and COG with other traits [18, 30-32].

2. Methods

2.1 Sample Description

2.1.1 Discovery samples—We obtained GWAS data (Table 1) as summary statistics (*p*-values and effect sizes). All participants were of European ancestry to ensure compatible linkage disequilibrium (LD) patterns. The datasets were controlled for systemic sample overlap to avoid potential bias. The COG data [19] (n = 269,867) was based on a GWAS meta-analysis from 14 epidemiological cohorts of European ancestry, that included healthy individuals, multiple age groups, and various correlated intelligence-related phenotypes. The cohorts either reported Spearman's *g* underlying several dimensions of cognitive functioning or a primary measure of fluid intelligence, highly correlated with *g*, see [19] for details.

The summary statistics for epilepsies [17] (n = 27,559 cases, 42,436 controls) were acquired from the International League Against Epilepsy (ILAE) Consortium and included data on the broad phenotypes 'all epilepsy', focal epilepsies and GGE as well as the focal subtypes 'lesion negative focal epilepsy', 'focal epilepsy with hippocampal sclerosis', 'focal epilepsy with lesions other than hippocampal sclerosis' and the generalized subtypes childhood absence epilepsy (CAE), juvenile absence epilepsy, juvenile myoclonic epilepsy (JME) and generalized tonic-clonic seizures. The sample sizes and the number of SNPs for all traits are given in Table 1.

All GWAS data underwent quality control and were formatted with the cleansumstats pipeline v1.6.0 [33].

2.1.2 Independent samples—To assess the reliability of our results, we also acquired GWAS summary statistics from independent samples of European ancestry. The independent epilepsies data was collected from FinnGen (freeze 9; https://r9.finngen.fi, phenotypic code G6_EPILEPSY) and consists of all epilepsies as a combined phenotype (n = 11,740 cases, 287,837 controls) [34]. We used an independent sample [35] from 23andMe, Inc. on educational attainment as a proxy for COG, as they are highly genetically correlated (r_g = 0.73) [19].

2.1.3 Ethics statement—All GWAS investigated in the present study were approved by the relevant ethics committees, and informed consent was obtained from all participants. The Regional Committee for Medical and Health Research Ethics for the South-East Norway found that no additional institutional review board approval was needed.

2.2 Data Analysis

2.2.1 Filtering of summary statistics—To avoid LD inflation, SNPs in the extended major histocompatibility complex (MHC), chromosome 8p23.1 and the microtubule-associated protein tau (MAPT) regions genome build GRCh37/hg19 locations chr6:25119106-33854733; chr8:7200000-12500000; chr17:40000000-47000000, respectively) were excluded in all analyses before fitting the statistical models [27, 36]. Excluding these long-range LD regions is specifically recommended for conjFDR analyses and MiXeR [27]. Here, we excluded them in all analyses to ensure consistent SNP selection during model fit. We note that conjFDR may still identify signals across all regions in the discovery phase.

2.2.2 Linkage disequilibrium score regression analysis—LDSC [25] was applied to estimate pairwise genetic correlations (r_g). LDSC estimates global genetic correlations and distinguishes between the contributions from polygenic effects and confounding factors. Multiple testing correction was carried out using the Benjamini-Hochberg method ($q < 0.05$).

2.2.3 Gaussian causal mixture models—We utilized univariate and bivariate Gaussian causal mixture models to GWAS data using MiXeR (v1.3) [24]. With maximum likelihood estimation, univariate MiXeR estimates the distribution of SNPs with non-null additive genetic effects beyond LD quantifying the number of causal variants explaining 90% of the SNP-heritability (polygenicity), and the variance of the effect sizes of the SNPs with non-null genetic effects (discoverability). Then, the SNP-heritability is computed on the observed scale based on the polygenicity and discoverability estimates. Further, bivariate MiXeR estimates the number of overlapping and phenotype-specific causal variants between two phenotypes.

All point estimates and standard deviations were computed by performing 20 iterations with 2 million randomly selected SNPs which were then further randomly pruned at a LD (r^2) threshold of 0.8, (resulting in ~600K SNPs per iteration). Akaike information criterion (AIC) and log-likelihood plots were evaluated for the model fit [24].

2.2.4 Conjunctional false discovery rate analysis—We applied the conjFDR analysis implemented in the pleioFDR software to increase genetic discovery of the shared loci between epilepsies and COG [26, 27]. The conjFDR analysis is an extension to the conditional false discovery rate (condFDR), which readjusts the test statistics in a primary phenotype (e.g., GGE) by conditioning on SNP associations with a secondary phenotype (e.g., COG). The conjFDR performs two condFDR analyses by first conditioning the primary phenotype on the secondary phenotype and then conditioning the secondary phenotype on the primary phenotype and selecting the conjFDR value as the maximum of the two condFDR values. The conjFDR threshold of 0.05 was used in line with previous studies [26, 27]. Using an LD threshold $r^2 = 0.01$, SNPs were randomly pruned over 500 iterations to avoid bias in the analysis [27].

The cross-trait enrichment is visualized by conditional quantile-quantile (Q-Q) plots, which plot p-value distributions for a primary phenotype for all SNPs, and for SNP strata defined

by their association with a secondary phenotype. A strong cross-trait enrichment is observed by a leftward deflection from the null hypothesis (diagonal) with a decrease in p-values in the Q-Q plots. For more details regarding condFDR/conjFDR, confer [26, 27].

2.2.5 Sign concordance test—To validate the conjFDR findings, we applied the sign concordance test in independent samples. We assessed the overall concordance in allelic effect directions of the lead SNPs for all identified loci between the discovery and the independent samples. For loci shared with more than one epilepsy phenotype, we used the most strongly associated lead SNP. The point estimates of the beta coefficients were compared to determine how many lead SNPs in the shared loci had concordant allelic directions in the discovery and the independent samples. Under the null hypothesis assumption, given that there is no genetic association with the trait of interest, the likelihood of randomly detecting sign concordance is 50%. We assessed if the observed sign concordance rates were significantly higher than expected (more than 50%) by a two-tailed, exact binomial test.

2.3 Functional Analyses

2.3.1 Genomic loci definition—Genomic loci were defined as independent if independent significant SNPs had r^2<0.60 and conjFDR<0.05 in accordance with the FUMA platform [37]. Lead SNPs were identified as independent significant SNPs with $r^2 < 0.1$ in approximate LD. All SNPs with conjFDR < 0.10 and in LD ($r^2 > 0.60$) with an independent significant SNP were chosen as the candidate SNPs. For merged loci within >250kb of each other, the SNP with the most significant conjFDR value was chosen as the lead SNP of the merged locus. Candidate SNPs in LD ($r^2 \geq 0.6$) with one of the independent SNPs in the locus defined the locus borders. All LD r^2 values were obtained from the 1000 Genomes Project European-ancestry haplotype reference panel [38].

The concordance of the shared loci was evaluated by studying their z-scores and odds ratios. Loci were identified as novel loci if at a minimum distance of 500kb from the reported loci from the original GWAS or not listed by the GWAS Catalog [39] or OpenTargets Genetics [40] or other GWAS analyses on epilepsies or COG.

2.3.2 Functional annotation—Combined annotation dependent depletion scores (CADD), regulomeDB scores and chromatin state scores were used to functionally annotate the candidate SNPs, in line with FUMA [37]. CADD score predicts deleterious SNP effects on proteins, regulomeDB score predicts the probability of a SNP to have a regulatory function and chromatin state scores predict transcriptional effects. We used the Variant-to-GENE (V2G) pipeline from OpenTargets Genetics, which incorporates gene distance, various molecular quantitative trait loci and chromatin interactions, to map lead SNPs to likely causal genes [40]. Gene expression and gene set analyses for the GO, KEGG and canonical pathways gene sets were carried out as hypergeometric tests using FUMA and Genotype-Tissue Expression data (GTEx) on the input of the mapped genes [41, 42]. The mapped genes were investigated using the National Center for Biotechnology Information database [43]. Using Brain RNA-Seq [44], we then leveraged the single-cell

RNA sequencing (RNA-Seq) data to assess whether the mapped genes were significantly expressed in brain cells.

3. Results

3.1 Linkage disequilibrium score regression analysis

Using LDSC [25], we estimated significant SNP-heritabilities of 0.19 for COG (h^2 SE= 6.80 x 10^{-3}), 0.12 for 'all epilepsy' (h^2 SE= 0.01), 0.07 for focal epilepsies (h^2 SE= 0.01) and 0.60 for GGE (h^2 SE= 0.05) (Supplementary Table 1). The focal epilepsy subtypes (h^2 range = 0.03 – 0.25) had lower estimated SNP-heritabilities compared to GGE subtypes (h^2 range = 0.60 – 0.93. Juvenile absence epilepsy and generalized tonic-clonic seizures were insufficiently powered for the analyses. Further, we found that five epilepsy phenotypes ('all epilepsy', focal epilepsies, 'lesion negative focal epilepsies', GGE and JME) were significantly negatively correlated with COG, in line with previous findings [16, 21, 22]. The significant genetic correlations between COG and 'lesion negative focal epilepsies' (r_g = −0.23, SE = 0.07, p = 3.00 x 10^{-4}) and between COG and JME (r_g = −0.12, SE = 0.04, p = 3.30 x 10^{-3}) are novel reports to our knowledge. The genetic correlations between COG and 'focal epilepsies with hippocampal sclerosis', 'focal epilepsies with lesions other than hippocampal sclerosis' and CAE did not reach significance.

3.2 MiXeR analysis

Univariate MiXeR [24] analyses were sufficiently powered for 'all epilepsy', GGE, CAE, JME and COG, as indicated by positive AIC scores (Supplementary Table 2). COG was estimated to be almost four times more polygenic than the four epilepsy phenotypes with similar polygenicities. Specifically, COG was estimated to be influenced by 11k (SD = 0.3k) variants, 'all epilepsy' by 2.9k (SD = 0.4k) variants, GGE by 2.9k (SD = 0.2k) variants, CAE by 2.5k (SD = 0.4k) variants and JME by 2.5k (SD = 0.3k) variants.

Applying bivariate MiXeR, we estimated the overlapping genomic proportion between COG and the four sufficiently powered epilepsy phenotypes and observed almost complete overlap with COG (Figure 1, Supplementary Table 3). 2.9k (SD = 0.4k) variants were estimated to be shared between COG and 'all epilepsy', 2.9k (SD = 0.2k) between COG and GGE, 2.3k (SD = 0.4k) between COG and CAE, and 2.3k (SD = 0.3k) between COG and JME. The fraction of concordant variants within the overlapping portion with COG was 0.37 for 'all epilepsy' (SD = 0.008), 0.42 for both GGE (SD = 0.007) and CAE (SD = 0.017), and 0.41 for JME (SD = 0.012); indicating mixed allelic effect directions among the overlapping variants, but an overabundance concordance rate below 0.50 of epilepsy risk variants linked to worse cognitive performance.

3.3 Conjunctional false discovery rate analysis

In line with the LDSC and MiXeR results, we observed substantial cross-trait enrichment between COG and the same four epilepsy phenotypes (GGE, JME, CAE and 'all epilepsy'), as visualized by the conditional Q-Q plots (Supplementary Figure 2). No cross-trait enrichment was observed for any of the focal epilepsies, generalized tonic-clonic seizures or juvenile absence epilepsy, likely reflecting insufficient statistical power.

Using conjFDR [26, 27], we leveraged the cross-trait enrichment and identified overlapping loci between COG and 'all epilepsy' (11), GGE (55), CAE (9) and JME (11) (Figure 2, Supplementary Tables 4-7). In total, we discovered five novel loci for 'all epilepsy', 27 novel loci for GGE, five novel loci for CAE and five novel loci for JME (Table 2). All COG loci have previously been reported [19, 20]. 15 of the identified loci were linked to at least two epilepsy phenotypes, while three loci were linked to at least three of the epilepsy phenotypes, specifically a locus at chromosome 2 near *CTD-2026C7.1* shared between 'all epilepsy', GGE, CAE and COG; a locus at chromosome 5 near *RP11-492A10.1* shared between GGE, CAE, JME and COG; and a locus at chromosome 10 near *C10orf76* shared between all of these epilepsy phenotypes and COG.

We determined the allelic effect directions of the lead SNPs for each locus. 21 out of 55 lead SNPs for GGE, one out of 11 lead SNPs for 'all epilepsy', five out of nine lead SNPs for CAE and four out of 11 lead SNPs shared with JME had concordant allelic effect directions.

3.4 Sign concordance test

For the distinct epilepsy loci identified at conjFDR < 0.05, 43 out of 63 (68%) lead SNPs were sign concordant in the independent epilepsy sample [34] (binomial test $p = 2.58 \times 10^{-3}$; Supplementary Table 8). For COG, 53 out of 66 (80%) lead SNPs were sign concordant in the independent proxy sample [35] ($p = 3.62 \times 10^{-7}$).

3.5 Functional annotation

Functional annotation of all candidate SNPs indicated that most of them are positioned in intronic (50%) and intergenic (27%) regions (Supplementary Tables 9-12). There were in total 23 nonsynonymous exonic variants located across 14 loci (Supplementary Table 13), implicating genes *LONRF2, STAB1, GNL3, ITIH1, CTD-2117L12.1, ELL2, RMI1, IER5L, FBXO3, SERPING1, DDN, TNRC6A, PER1, UPK1A, ZNFX1* and *BRWD1*. Across analyses, 54 candidate SNPs had a CADD score higher than 12.37 which indicates deleteriousness[45]. We applied OpenTargets to map genes to each lead SNP based on their V2G scores (Supplementary Tables 14-17). While the mapped genes were not significantly associated with any gene set, they were significantly enriched for expression in several brain regions: particularly the anterior cingulate cortex, frontal cortex, cortex, hippocampus, amygdala, and the basal ganglia structures caudate nucleus, putamen, and nucleus accumbens (Supplementary Figure 3). Finally, we determined the cell type-specific expression of the mapped genes in the human brain using Brain RNA-Seq [44], revealing most of them were highly expressed in at least one type of brain cell investigated (Supplementary Figures 6-9).

4. Discussion

In this study, we utilized the largest available GWASs on common epilepsies and COG to provide new insights into their genetic relationship. Using MiXeR, we estimated substantial genetic overlap between COG and the four epilepsy phenotypes 'all epilepsy', GGE, JME and CAE (Figure 1), in which almost all epilepsy risk variants were found to also affect cognitive performance. Moreover, using conjFDR we identified 66 distinct genomic loci

shared between epilepsies and COG (Figure 2). Among these, five loci were novel for 'all epilepsy', 27 for GGE, five for CAE and five for JME (Table 2, Supplementary Tables 4-7). Taken together, our study extends previous work by estimating extensive genetic overlap between several epilepsy phenotypes and COG, and we dissect their shared genetic basis by identifying several novel shared loci.

Using MiXeR, we estimated COG to be almost four times more polygenic than the epilepsy phenotypes 'all epilepsy', GGE, JME and CAE. As such, the estimated overlap represents a considerably smaller portion of the genetic architecture of COG than of the epilepsy phenotypes. While the majority of epilepsy risk variants were associated with lower cognitive performance, a large fraction of the epilepsy variants were associated with higher cognitive performance, indicating a complex genetic relationship between epilepsy and COG. The 'all epilepsy' category, which also includes focal epilepsies, displayed the largest negative genetic association with COG, in line with focal epilepsies being more strongly associated with cognitive impairment than generalized epilepsies, at least at the genetic level [16, 17, 21-23]. Overall, the findings are consistent with the wide distribution of cognitive performance observed among individuals with epilepsy [5, 7], suggesting potential subgroups of epilepsy patients with differential genetic tendencies for higher or lower cognitive functioning, which may also relate to other predictive factors such as the onset and frequency of seizures of psychiatric comorbidity [8, 18].

The results reflect the known genetic heterogeneity across common epilepsies [16, 17], particularly the considerably smaller SNP-heritability estimates of focal epilepsies (h^2 range = 0.03 – 0.25) compared to the GGE types (h^2 range = 0.59 – 0.95), which affected the ability to detect genetic overlap. The combination of relatively small GWAS samples and/or low SNP-heritability for the focal epilepsies leads to insufficiently powered MiXeR and conjFDR analyses. While JME (h^2 = 0.93, SE = 0.12) and CAE (h^2 = 0.79, SE = 0.16) had larger SNP-heritability estimates than GGE (h^2 = 0.60, SE = 0.05), the larger sample size for GGE yielded more power for conjFDR analyses. Accordingly, the greater part (83%) of the identified shared loci was linked to GGE. Thus, caution should be exercised when interpreting the present results.

Among the overlapping loci, 15 loci were shared between at least two epilepsy types. A locus on chromosome 10 was significantly associated with all four epilepsy phenotypes and had the strongest association of all loci identified (top lead SNP rs11191116, conjFDR = 9.14×10^{-9} for COG and GGE), in which epilepsy risk was associated with lower cognitive performance (Supplementary Tables 4-7). This locus reached genome-wide significance in all epilepsy phenotypes and COG [17, 19]. Our gene mapping approach implicated *KCNIP2* for this locus (Supplementary Tables 14-17), which encodes a member of the voltage-gated potassium channel-interacting proteins (KCNIPs) [43]. This channel has recently been identified as a key regulator of homeostatic excitability in humans, and deletion leads to increased susceptibility to epilepsy and increased excitability in pyramidal hippocampal neurons [46]. We also observed other mapped genes from the shared loci linked to membrane transport and signal transduction (*CACNA1E, CD47, SLC5A11, SLC24A2, CABP1, CPNE1*). Moreover, many mapped genes are involved in transcription regulation (*SOX11, SOX14, HMGN1, TCEA3, ELL2, SP4*), neurodevelopmental processes

(*KIFBP, SEMA3F, and NCAM1*), and serine/threonine kinase processes (*PTPA, VRK2* and *STRADA*) [43]. To our knowledge, 12 of these are novel associations for epilepsy (*CACNA1E, SLC5A11, SLC24A2, CABP1, SOX11, HMGN1, TCEA3, SP4, KIFBP, NCAM1, PTPA* and *STRADA*). In our previous GWAS study identifying shared loci between epilepsy and psychiatric disorders, we also observed several genes encoding serine/threonine kinases [18]. Serine/threonine kinases are vital in regulating neuronal and synaptic activity, including neurotransmitter transport [47]. Furthermore, among the 38 novel loci identified, six contained nonsynonymous exonic variants, within genes *LONRF2, FBXO3, TNRC6A, BRWD1, IER5L* and *SERPING1*. Nonsynonymous exonic variants are more likely to substantially affect a phenotype by disrupting protein function. The strongest novel association detected in our analysis was identified on chromosome 21 top lead SNP rs13339986, conjFDR = 3.9×10^{-3} shared between GGE and COG, in which epilepsy risk was associated with higher cognitive performance (Table 2). The locus was also shared with CAE and included the nonsynonymous exonic variant within *BRWD1*, which encodes a member of the WD repeat family that regulates various cellular functions including signal transduction and cellular differentiation, and plays a role in neurodevelopment [48].

To clarify, the cross-trait shared genetic signals may reflect both shared or separate causal variants in strong LD with each other, which conjFDR analysis cannot distinguish [27]. Hence, further experimental validation is required to determine how the identified genetic variants impact cognitive performance and the risk of epilepsies. Nevertheless, with functional annotation, we marked several candidate SNPs that may be plausible causal variants in the shared loci for follow-up studies. Moreover, to improve statistical power for the insufficiently powered epilepsy types, the research community should continue their focus on assembling larger GWAS samples on these phenotypes, in combination with advanced genomic methods that enhance genomic discovery [27, 49]. As future GWAS samples get larger, shared loci between multiple epilepsy types and COG are likely to be identified, given the shared genetic signal across common epilepsies. Of note, GWAS summary statistics do not provide access to individual level data but represent the population average for each phenotype. Analysis of more deeply phenotyped cohorts of epilepsy patients, including detailed assessments of cognitive ability, may help further dissect the shared genetic relationship between COG and epilepsy, and clarify the presence of potential subgroups among epilepsy patients, who may be characterized by distinct risk profiles and clinical features. Another limitation was the use of European ancestry datasets to avoid LD bias in conjFDR analyses. To ensure generalizability of the results, it is paramount that more diverse ancestries are adequately represented in future GWAS datasets, which is necessary for enabling precision medicine approaches in clinical neurology [50].

5. Conclusion

Overall, we further dissect the shared genetic basis of COG and epilepsy by demonstrating polygenic overlap between several epilepsy types and COG with significant negative correlations. Additionally, we discover multiple novel shared genomic loci between these phenotypes, which may inform the understanding of the shared molecular genetic mechanisms underlying these phenotypes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This work was performed on Services for Sensitive Data (TSD), University of Oslo, Norway, with resources provided by UNINETT Sigma2 - the National Infrastructure for High Performance Computing and Data Storage in Norway.

The project is funded by ERA-NET-NEURON (Application no: ES609126, Project NMDAR-PSY) which is funded by participating Research Councils across Europe. The work was supported by the Research Council of Norway (262656, 249711, 248980, 248778, 226971, 223273, 300309, 324252, 324499, 326813 and 334920), South-East Norway Regional Health Authority (2016–064, 2022-073 and 2022-087), KG Jebsen Stiftelsen (SKGJ-MED-008), European Union's Horizon 2020 Research and Innovation Programme (847776, CoMorMent; 964874, RealMent; and 801133, Marie Sklodowska-Curie Actions) and EAA grant (#EEA-RO-NO-2018-0573). K.S.O., G.K. and A.M.D. were supported by NIH (K.S.O: 5R01MH124839-02; G.K.: R01MH123724-01; A.M.D.: U24DA041123, R01AG076838, U24DA055330, and OT2 HL161847). S.B. was supported by Norwegian Health Association (22731).

Data availability statement

GWAS summary statistics except 23andMe, Inc. used in this study are publicly available and can be accessed through the original publications.

The study was conducted using the following software and tools:

- MiXeR (github.com/precimed/mixer/commit/f56a44, https://github.com/comorment/mixer/tree/v1.3.0)
- CondFDR & ConjFDR (https://github.com/precimed/pleiofdr/commit/846441)
- LDSC (https://github.com/bulik/ldsc; github.com/comorment/ldsc/commit/f2d7d6)
- FUMA (https://fuma.ctglab.nl/)
- OpenTargets Genetics (https://genetics.opentargets.org/)
- Cleansumstats (https://github.com/BioPsyk/cleansumstats/tree/1.6.0)
- Brain RNA-Seq (https://brainrnaseq.org/)
- MATLAB R2017a (https://se.mathworks.com)

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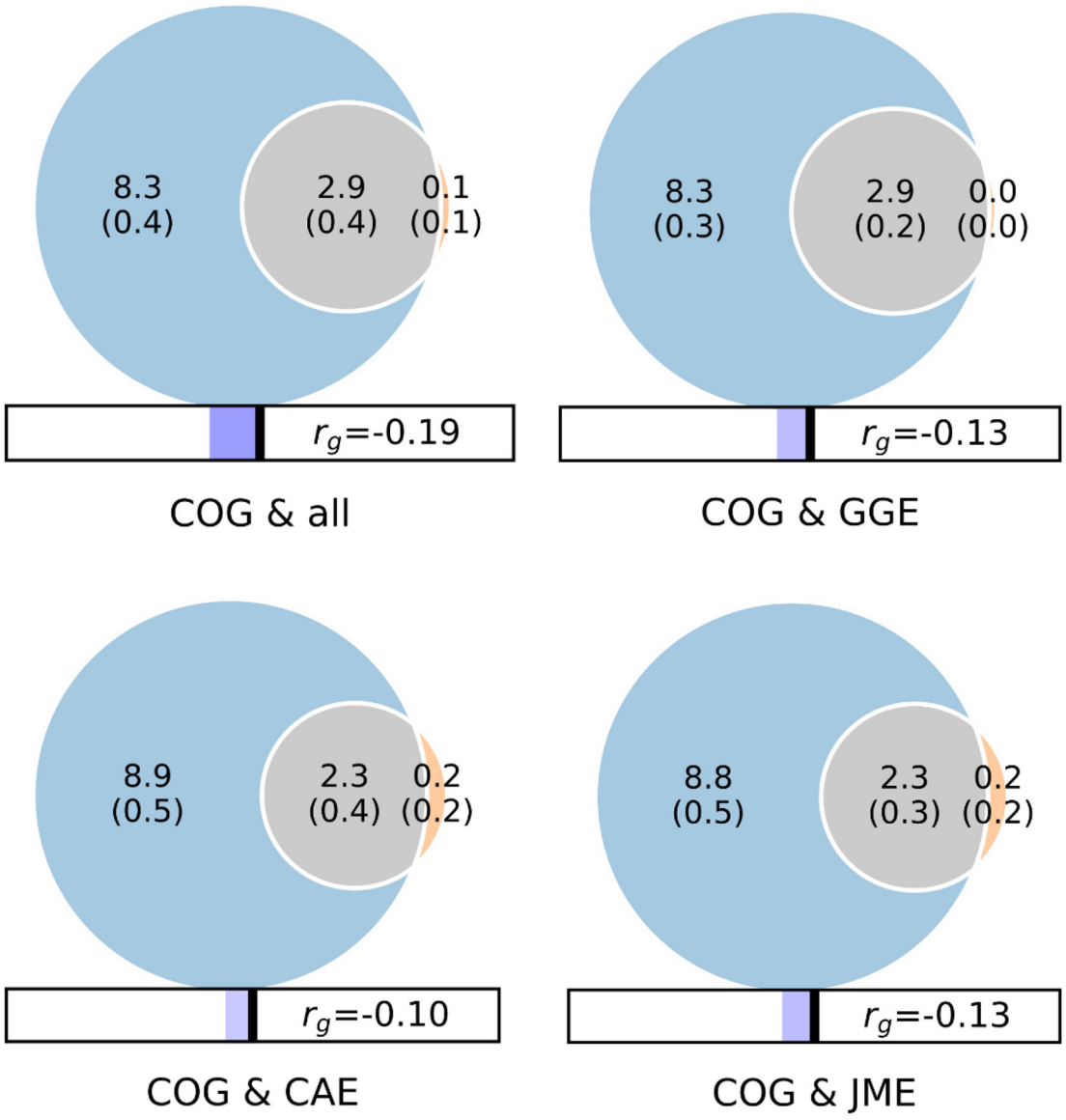

Figure 1. Genome-wide genetic overlap and genetic correlations between general cognitive ability (COG) and epilepsies ('all epilepsy', GGE, JME, CAE).

The numbers in the Venn diagrams represent the number of shared and phenotype-specific trait-influencing variants which account for 90% of SNP-heritability in thousands, and r_g represents genome-wide genetic correlations. Abbreviations: COG, general cognitive ability; ALL, 'all epilepsy'; GGE, genetic generalized epilepsies; JME, juvenile myoclonic epilepsy; CAE, childhood absence epilepsy)

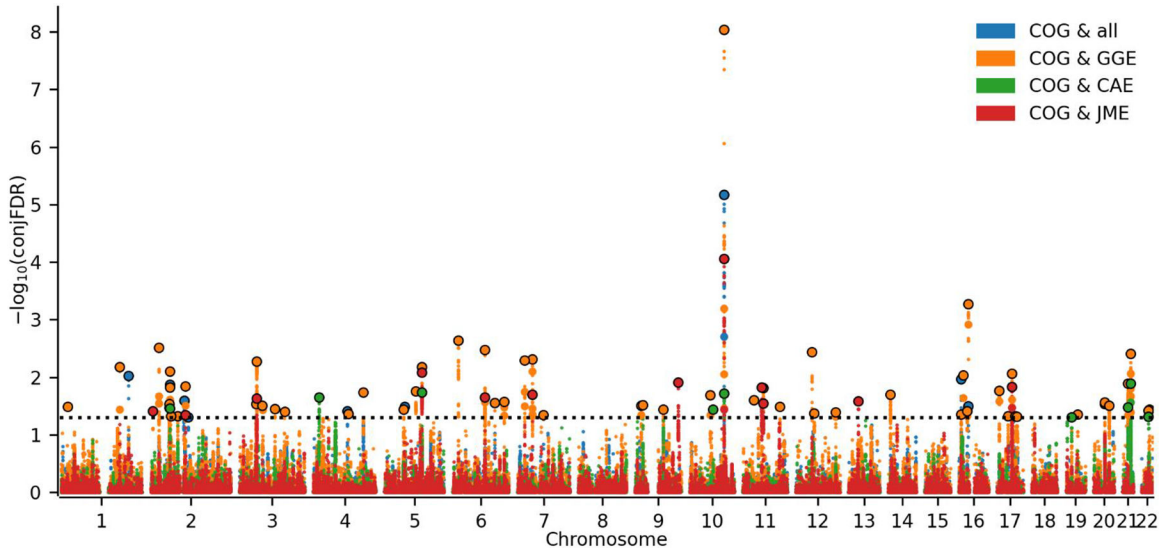

Figure 2. Common genetic variants jointly associated with COG and epilepsies ('all epilepsy', GGE, JME and CAE) at conjunctional false discovery rate (conjFDR) < 0.05.

Manhattan plots showing the −log10 transformed conjFDR values for each single nucleotide polymorphism (SNP) on the y-axis and chromosomal positions along the x-axis. The dotted line represents the conjFDR threshold for significant association < 0.05. Abbreviations: COG, general cognitive ability; ALL, 'all epilepsy'; GGE, genetic generalized epilepsies; JME, juvenile myoclonic epilepsy; CAE, childhood absence epilepsy)

TABLE 1.

Summary Data from all GWAS used in the present study.

Phenotype	Sample size, n	SNPs, n	Source
Discovery Samples			
All epilepsy	27,559 cases, 42,436 controls	4,137,194	ILAE [17]
Focal epilepsies	14,939 cases, 42,436 controls	4,121,249	ILAE [17]
Genetic generalized epilepsies	6,952 cases, 42,436 controls	4,123,710	ILAE [17]
Focal epilepsy with hippocampal sclerosis (HS)	1,260 cases, 42,436 controls	3,900,814	ILAE [17]
Lesion negative focal epilepsy	5,778 cases, 42,436 controls	3,975,365	ILAE [17]
Focal epilepsy with lesions other than HS	4,213 cases, 42,436 controls	4,006,969	ILAE [17]
Childhood absence epilepsy	1,049 cases, 42,436 controls	4,220,933	ILAE [17]
Juvenile absence epilepsy	662 cases, 42,436 controls	4,225,222	ILAE [17]
Juvenile myoclonic epilepsy	1,732 cases, 42,436 controls	4,223,181	ILAE [17]
Generalized tonic-clonic seizures	485 cases, 42,436 controls	4,214,303	ILAE [17]
General cognitive function	269,867	8,002,022	Savage et al [19]
Independent Samples			
All epilepsy	11,740 cases, 287,837 controls	14,614,037	FinnGen (R9)
Educational Attainment	76,155	9,108,400	Okbay et al [35]

Abbreviations: ILAE, International League Against Epilepsy Consortium

TABLE 2.

All novel loci associated with epilepsies at conjFDR<0.05.

Shared between	CHR	Lead SNP	A1/A2	Nearest Gene	OpenTargets Gene	P-Value	Concord Effect
GGE & COG	1	rs61777153	G/A	TCEA3	TCEA3	2.53E-04	Yes
	1	rs3843280	A/G	CACNA1E	CACNA1E	2.05E-05	Yes
	2	rs45600937	G/A	BCL11A	BCL11A	5.02E-04	Yes
	3	rs62253001	A/G	MITF	MITF	2.25E-04	Yes
	4	rs7679673	C/A	AC004069.2	PPA2	4.18E-04	No
	4	rs1107797	T/C	PET112	GATB	9.88E-05	No
	5	rs62366404	G/A	PLK2	GAPT	2.05E-04	No
	6	rs6569342	C/T	RP11-436D23.1	N/A	7.36E-06	No
	7	rs2237303	A/G	SP4	SP4	1.35E-05	No
	7	rs10243354	T/G	ZMIZ2	ZMIZ2	1.27E-05	Yes
	7	rs7785241	C/T	MAGI2	MAGI2	2.76E-04	Yes
	9	rs4977551	A/G	SLC24A2	SLC24A2	3.52E-05	No
	9	rs6475737	G/A	SUMO2P2	ELAVL2	2.31E-04	No
	10	rs10509112	C/T	CCDC6	CCDC6	3.99E-05	No
	11	rs1402954	C/T	FBXO3	FBXO3	1.11E-04	No
	11	rs7938812	T/G	NCAM1	NCAM1	2.56E-04	No
	12	rs773107	A/G	RAB5B	RAB5B	4.09E-04	No
	12	rs473121	T/C	CABP1	CABP1	3.84E-04	No
	14	rs17111366	A/G	NOVA1	NOVA1	1.13E-04	No
	16	rs9937737	C/T	U95743.1	ERCC4	2.62E-05	No
	16	rs7186893	G/T	TNRC6A	SLC5A11	3.56E-04	No
	17	rs2632519	A/G	BZRAP1-AS1:SUPT4H1	MPO	4.95E-04	No
	17	rs8075273	C/A	MAP3K3	STRADA	4.80E-04	Yes
	20	rs7270848	A/G	ARFGEF2	CSE1L	2.36E-04	Yes
	21	rs13339986	T/C	BRWD1	PSMG1	9.31E-06	Yes
	22	rs743942	G/A	RP3-434P1.6	KDELR3	2.13E-04	No
	22	rs139064	C/T	MKL1	MRTFA	3.12E-04	Yes
ALL & COG	1	rs10158414	T/C	CR1:RP11-78B10.2	CR1	9.97E-06	No
	2	rs7559464	G/A	LONRF2	LONRF2	4.15E-05	No
	2	rs2222131	G/T	NT5DC4	SLC20A1	1.14E-04	No
	4	rs173048	A/C	SLC39A8	SLC39A8	7.73E-05	No
	5	rs36033	T/C	C5orf64:RP11-2O17.2	ZSWIM6	5.89E-05	No
CAE & COG	4	rs16895737	A/C	FAM184B	DCAF16	5.50E-05	Yes
	10	rs16925839	T/C	STOX1	KIFBP	1.09E-04	Yes
	19	rs11666808	C/T	KIAA1683	IQCN	6.33E-05	Yes
	21	rs12626405	T/G	BRWD1	HMGN1	2.70E-05	Yes
	22	rs111959380	G/A	RP3-434P1.6	KDELR3	1.68E-04	No

Shared between	CHR	Lead SNP	A1/A2	Nearest Gene	OpenTargets Gene	P-Value	Concord Effect
JME & COG	2	rs7598861	G/A	AC107057.2:AC108025.2	SOX11	1.44E-04	Yes
	6	rs2450510	G/A	RP11-436D23.1	N/A	6.38E-05	No
	7	rs4724319	A/G	ZMIZ2	ZMIZ2	5.42E-05	Yes
	9	rs184457	G/A	IER5L:RP11-247A12.2	PTPA	2.86E-05	No
	11	rs10750866	A/G	AP000662.4	SERPING1	3.69E-05	Yes

P-Values are reported for the epilepsy phenotype. Novelty is considered for the particular epilepsy type in analysis. Detailed information about the reported loci can be found in Supplementary tables 4-7. Abbreviations: COG, general cognitive ability; All, ‘all epilepsy’; GGE, genetic generalized epilepsies; CAE, childhood absence epilepsy; JME, juvenile myoclonic epilepsy.