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Identification of novel genomic risk loci shared between common epilepsies and psychiatric disorders

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Psychiatric disorders and common epilepsies are heritable disorders with a high comorbidity and overlapping symptoms. However, the causative mechanisms underlying this relationship are poorly understood. Here we aimed to identify overlapping genetic loci between epilepsy and psychiatric disorders to gain a better understanding of their comorbidity and shared clinical features.

We analysed genome-wide association study data for all epilepsies ($n = 44\,889$), genetic generalized epilepsy ($n = 33\,446$), focal epilepsy ($n = 39\,348$), schizophrenia ($n = 77\,096$), bipolar disorder ($n = 406\,405$), depression ($n = 500\,199$), attention deficit hyperactivity disorder ($n = 53\,293$) and autism spectrum disorder ($n = 46\,350$). First, we applied the MiXeR tool to estimate the total number of causal variants influencing the disorders. Next, we used the conjunctional false discovery rate statistical framework to improve power to discover shared genomic loci. Additionally, we assessed the validity of the findings in independent cohorts, and functionally characterized the identified loci.

The epilepsy phenotypes were considerably less polygenic (1.0 K to 3.4 K causal variants) than the psychiatric disorders (5.6 K to 13.9 K causal variants), with focal epilepsy being the least polygenic (1.0 K variants), and depression having the highest polygenicity (13.9 K variants). We observed cross-trait genetic enrichment between genetic generalized epilepsy and all psychiatric disorders and between all epilepsies and schizophrenia and depression. Using conjunctional false discovery rate analysis, we identified 40 distinct loci jointly associated with epilepsies and psychiatric disorders at conjunctional false discovery rate <0.05, four of which were associated with all epilepsies and 39 with genetic generalized epilepsy. Most epilepsy risk loci were shared with schizophrenia ($n = 31$). Among the identified loci, 32 were novel for genetic generalized epilepsy, and two were novel for all epilepsies. There was a mixture of concordant and discordant allelic effects in the shared loci. The sign concordance of the identified variants was highly consistent between the discovery and independent datasets for all disorders, supporting the validity of the findings. Gene-set analysis for the shared loci between schizophrenia and genetic generalized epilepsy implicated biological processes related to cell cycle regulation, protein phosphatase activity, and membrane and vesicle function; the gene-set analyses for the other loci were underpowered.

The extensive genetic overlap with mixed effect directions between psychiatric disorders and common epilepsies demonstrates a complex genetic relationship between these disorders, in line with their bi-directional relationship, and indicates that overlapping genetic risk may contribute to shared pathophysiological and clinical features between epilepsy and psychiatric disorders.

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Introduction

Brain disorders are major global causes of morbidity with high costs for society.[1] Epilepsy is regarded as a heterogeneous neurological condition defined by recurrent seizures, affecting over 60 million people worldwide.[1,2] Psychiatric comorbidity is frequent in people with epilepsy, including depression, anxiety, bipolar disorder, psychosis, attention deficit hyperactivity disorder (ADHD), and autism spectrum disorders (ASD).[3,4] These comorbidities share some clinical features with epilepsy, may impede diagnostic accuracy and treatment approaches, and are associated with a lower quality of life for people with epilepsy.[3,4] The relationship between epilepsy and psychiatric disorders seems to be bi-directional and the underlying aetiological mechanisms are poorly understood.[3–5] Certain anti-seizure medications (valproate, lamotrigine and carbamazepine) are among the most effective drugs for treating bipolar disorder, suggesting shared biological mechanisms between epilepsy and bipolar disorder.[6] Other anti-seizure medications are known to induce psychiatric adverse effects, while anti-psychotic drugs may alter seizure threshold.[6,7] Potential shared neurobiological dysfunctions have been implicated across these disorders, such as perturbed calcium signalling, synaptic plasticity and neurotransmission.[8–11] Uncovering shared genetic variants for epilepsy and psychiatric disorders may help identify people at risk and guide early treatment decisions.

Both psychiatric disorders and epilepsy are heritable.[12–14] The heritability accounted for by common single nucleotide polymorphisms (SNPs) is estimated to range between 11% and 24% for depression, ADHD, ASD, bipolar disorder and schizophrenia.[15–19] Epilepsy is broadly categorized under the two major subtypes, focal epilepsy and generalized epilepsy; the latter being primarily constituted by genetic generalized epilepsy (GGE). Focal epilepsy and GGE have substantial differences in their SNP heritability estimates, 9.2% and 32.1%, respectively, reflecting their different aetiologies.[2] Recent large-scale genome-wide association studies (GWAS) have identified 287 risk loci for schizophrenia, 64 loci for bipolar disorder, 178 loci for depression, 27 loci for ADHD, five loci for ASD and 26 loci for common epilepsies.[2,15–25] Further, two risk loci were recently identified as shared between ADHD and GGE.[26] However, these loci only account for a small fraction of the SNP heritabilities. GWAS analyses have also indicated a high degree of shared genetic risk between psychiatric disorders, with substantial pairwise genetic correlations estimated between schizophrenia, bipolar disorder, depression, ADHD and ASD.[27,28] A significant yet weak positive genome-wide correlation was recently reported between GGE and ADHD, indicating shared genetic risk, while weak negative genetic correlations between epilepsy phenotypes, schizophrenia and bipolar disorder did not survive correction for multiple comparisons.[25,26] No significant genetic correlations were reported between epilepsies and depression or ASD. However, the estimates of genetic correlations do not provide a complete overview of genetic overlap between complex human phenotypes.[29,30] First, genetic correlations are agnostic about the specific shared loci involved, and accumulating evidence has demonstrated substantial genetic overlap between complex human phenotypes despite weak or absent genetic correlations,[29,31–33] including between psychiatric and neurological disorders.[34–36]

In the present study, we aimed to improve the understanding of the genetic relationship between common epilepsies and major psychiatric disorders using MiXeR,[37] which quantifies the number of variants influencing a phenotype, and the conjunctional false discovery rate (conjFDR) approach, which boosts GWAS discovery

by leveraging overlapping GWAS associations to identify shared genomic loci.[30,38] This approach has improved discovery of shared genetic influences between several complex human phenotypes in recent years.[30,32–36,39–42]

Materials and methods

Sample description

GWAS data were obtained as summary statistics (*P*-values and effect sizes; Table 1). For each phenotype, available GWAS data with the largest sample size were chosen and overlapping samples were excluded, which might otherwise bias conjFDR results. In total, we analysed GWAS data on more than one million participants (258 230 cases and 773 053 controls).

The GWAS data on all epilepsies combined, focal epilepsy and GGE were obtained from the International League Against Epilepsy (ILAE) Consortium.[2] GWAS data for schizophrenia[19] and bipolar disorder[18] were obtained from the Psychiatric Genomics Consortium (PGC). Depression data were obtained from a meta-analysis[17] of data from PGC and 23andMe, Inc. Data on both ADHD[15] and ASD[16] were acquired from PGC and the iPSYCH cohort. The GWAS participants were predominantly of European ancestry.

All GWAS investigated in the present study were approved by the relevant ethics committees, and informed consent was obtained from all participants. The Norwegian Institutional Review Board for the South-East Norway Region has evaluated the current protocol and found that no additional institutional review board approval was needed because no individual data were used. See Supplementary material for more details.

Data analysis

Univariate causal mixture model: MiXeR

We applied the statistical tool, MiXeR v1.3, to estimate the number of causal variants explaining 90% of the SNP heritability of each phenotype, i.e. the polygenicity, using GWAS summary statistics.[37] A 'causal' variant is here defined as a variant with non-zero additive genetic effects on a phenotype.[37] Akaike information criterion (AIC) was used to evaluate the model fit. More information on the MiXeR method can be found in the Supplementary material.

Conjunctional false discovery rate analysis

We applied the conjFDR method to increase discovery of genomic loci jointly associated with epilepsies and psychiatric disorders. The conjFDR approach is an extension of the conditional FDR (condFDR), which leverages cross-trait enrichment between two phenotypes to improve genetic discovery[30,38] CondFDR readjusts the test statistics in a primary phenotype (e.g. GGE) by conditioning on SNP associations with a secondary phenotype (e.g. schizophrenia). The conjFDR method performs two condFDR analyses (conditioning the first phenotype on the second phenotype and vice versa) and defines the conjFDR value as the maximum of the two condFDR values. The conjFDR threshold 0.05 was used in line with previous literature.[30,38] The cross-trait enrichment is visualized using conditional Q-Q plots, which show the distribution of *P*-values for a primary phenotype for all SNPs, and for SNP strata defined by their association with the secondary phenotype. We excluded SNPs around the extended major histocompatibility complex (MHC) region, chromosome 8p23.1 and *MAPT* region (genome build 19 locations chr6:25119106-33854733; chr8:7200000-12500000; chr17:40000000-47000000, respectively) before fitting the FDR model to avoid bias in our cond/conjFDR analyses due to their complex regional linkage disequilibrium (LD)[45] (Supplementary material).

Functional analyses

Genomic loci definition

Independent genomic loci were defined in line with the FUMA[46] protocol. Independent significant SNPs were identified as $r^2 < 0.60$ and conjFDR < 0.05. Of those, SNPs with $r^2 < 0.1$ were defined as in approximate linkage equilibrium and chosen as lead SNPs. Candidate SNPs were defined as SNPs with a conjFDR value of <0.10 and an LD r^2-value of >0.60 with an independent significant SNP. All loci < 250 kb apart were merged and the SNP with the most significant conjFDR value was chosen as the lead SNP of the merged locus. The borders of the loci were defined by identifying all candidate SNPs in LD ($r^2 \geq 0.6$) with one of the independent

Table 1 Summary data from all GWAS used in the present study

Phenotype	Sample size, *n*	Ancestry (*n*)	SNPs, *n*	Source
Discovery samples				
All epilepsy	15 212 cases, 29 677 controls	86% European (38 752), 8% Asian (3406), 6% African (2731)	4 880 492	ILAE[2]
Focal epilepsy	9671 cases, 29 677 controls	84% European (33 313), 9% Asian (3365), 7% African (2670)	4 862 782	ILAE[2]
GGE	3769 cases, 29 677 controls	83% European (27 926), 9% Asian (2875), 8% African (2645)	4 867 068	ILAE[2]
SCZ	45 313 cases, 67 472 controls	European	7 634 648	Trubetskoy *et al.*[19]
BIP	39 027 cases, 367 378 controls	European	9 028 988	Mullins *et al.*[18]
DEP	121 198 cases, 246 363 controls	European	15 807 881	Howard *et al.*[17]
ADHD	19 099 cases, 34 194 controls	European	8 094 094	Demontis *et al.*[15]
ASD	18 381 cases, 27 969 controls	European	9 112 386	Grove *et al.*[16]
Independent samples				
All epilepsy	2466 cases, 175 788 controls	European	15 746 420	https://r5.finngen.fi
SCZ	22 778 cases, 35 362 controls	East Asian	10 694 910	Lam *et al.*[22]
BIP	4501 cases, 192 220 controls	European	15 746 437	https://r5.finngen.fi
DEP	170 756 cases, 329 443 controls	European	15 746 508	https://r5.finngen.fi
ADHD	4224 cases, 203 345 controls	European	6 981 749	MoBa; Magnus *et al.*[43,44]
ASD	925 cases, 206 644 controls	European	6 981 749	MoBa; Magnus *et al.*[43,44]

BIP = bipolar disorder; DEP = depression; SCZ = schizophrenia; ILAE = International League Against Epilepsy; MoBa = Norwegian Mother, Father and Child Cohort Study.

significant SNPs in the locus. All LD r^2-values were obtained from the 1000 Genomes Project European-ancestry haplotype reference panel.[47]

We evaluated the directional effects of the shared loci by comparing their z-scores and odds ratios. Novel loci were defined as novel if they were not within 500 kb of the reported loci from the original GWAS or were not reported in the GWAS Catalogue[48] or other post-GWAS analyses on epilepsy or psychiatric disorders.

Functional annotation

SNPs were functionally annotated with combined annotation dependent depletion scores (CADD), regulomeDB scores and chromatin states. These scores predict deleterious SNP effect on a protein, likelihood of regulatory functionality and transcriptional effects due to chromatin states, respectively. The candidate SNPs were mapped to putative causal genes using positional mapping, expression quantitative trait locus (eQTL) mapping and chromatin interaction mapping.[46] Gene expression and gene-set analysis of the identified genes were performed using FUMA and GenotypeTissue Expression data (GTEx)[46,49] (Supplementary material).

Validation tests in independent samples

To validate our findings, we conducted sign concordance tests[50] to compare the overall pattern of consistency in allelic effect directions of the lead SNPs between discovery and independent datasets on schizophrenia[22] from PGC, bipolar disorder,[51] depression,[51] epilepsy combined[51] from FinnGen, and ADHD and ASD[43,44] from the Norwegian Mother, Father and Child Cohort Study (MoBa) conducted by the Norwegian Institute of Public Health (Table 1). To secure sufficient number of variants for valid analysis, we evaluated loci identified at a more relaxed significance threshold (conjFDR <0.10). We determined the number of lead SNPs in the shared loci that had the same allelic effect direction in the independent datasets by comparing the point-estimate of the beta coefficients. Under the null hypothesis that there is no genetic association with the trait of interest, observing sign concordance by chance has a probability of 50%. Using the two-tailed exact binomial test, we then evaluated whether the observed sign concordance rates were significantly higher than expected by chance.

Data availability and computational tools

Statistical analyses for the relevant methods were performed in MATLAB and Python, using existing tools available on GitHub, including MiXeR v1.3 (https://github.com/precimed/mixer) and condFDR/conjFDR (https://github.com/precimed/pleiofdr).

Results

MiXeR results

Using MiXeR,[37] we estimated the number of 'causal' variants for each epilepsy phenotype and found that ~3.0 K variants [standard deviation (SD) = 0.8 K] influence all epilepsy, ~3.4 K variants (SD = 0.3 K) influence GGE and ~1.0 K variants (SD = 1.1 K) influence focal epilepsy; reflecting their different genetic architectures (Table 2). The polygenicity estimates for psychiatric disorders were 9.6 K variants for schizophrenia (SD = 0.2 K), 8.6 K variants for bipolar disorder (SD = 0.2 K), 13.9 K variants for depression (SD = 0.6 K), 5.6 K variants for ADHD (SD = 0.4 K) and 12.3 K variants for ASD (SD = 1.5 K) (Table 2), in line with previous reports.[13–15] The large standard deviations for the polygenicity estimates for focal epilepsy and ASD indicate that these estimates should be interpreted with caution, likely reflecting a combination of low SNP-heritability and insufficient GWAS power for these disorders. Moreover, we estimated the discoverability of each disorder and found that depression (7.43×10^{-6}, SD = 2.65×10^{-7}) and ASD (2.45×10^{-5}, SD = 2.98×10^{-6}) were the least discoverable disorders, while focal epilepsy (1.11×10^{-4}, SD = 3.35×10^{-5}) and GGE (2.57×10^{-4}, SD = 1.89×10^{-5}) were the most discoverable traits (Table 2).

Cross-trait enrichment

The conditional Q-Q plots demonstrated substantial enrichment of SNP associations with GGE as a function of increasing levels of SNP associations with all psychiatric disorders, indicating polygenic overlap (Fig. 1). This enrichment was also consistent in the reverse conditional Q-Q plots (Supplementary Fig. 1). We also observed bidirectional cross-trait enrichment between all epilepsies and schizophrenia and depression, but not with the other disorders (Supplementary Figs 2 and 3). We observed enrichment of SNP associations with bipolar disorder conditional on focal epilepsy, but not in the other direction (Supplementary Figs 4 and 5). There was no

Table 2 Univariate MiXeR estimates for the epilepsies and psychiatric disorders

Phenotype	ADHD	ASD	BIP	DEP	SCZ	EP	FEP	GGE
pi (mean)	1.76×10^{-3}	3.88×10^{-3}	2.71×10^{-3}	4.38×10^{-3}	3.00×10^{-3}	9.48×10^{-4}	3.04×10^{-4}	1.07×10^{-3}
pi (SD)	1.37×10^{-4}	4.75×10^{-4}	7.43×10^{-5}	1.79×10^{-4}	7.56×10^{-5}	2.59×10^{-4}	3.33×10^{-4}	9.47×10^{-5}
sig2_beta (mean)	6.31×10^{-5}	2.45×10^{-5}	3.37×10^{-5}	7.43×10^{-6}	6.13×10^{-5}	6.15×10^{-5}	1.11×10^{-4}	2.57×10^{-4}
sig2_beta (SD)	4.59×10^{-6}	2.98×10^{-6}	8.52×10^{-7}	2.65×10^{-7}	1.43×10^{-6}	1.58×10^{-5}	3.35×10^{-5}	1.89×10^{-5}
sig2_zero (mean)	1.09×10^{0}	1.02×10^{0}	1.12×10^{0}	1.05×10^{0}	1.22×10^{0}	1.19×10^{0}	1.17×10^{0}	1.13×10^{0}
sig2_zero (SD)	2.98×10^{-3}	5.89×10^{-4}	3.01×10^{-3}	5.95×10^{-4}	4.36×10^{-3}	1.57×10^{-3}	9.32×10^{-4}	1.64×10^{-3}
h2 (mean)	2.29×10^{-1}	1.95×10^{-1}	1.89×10^{-1}	6.74×10^{-2}	3.82×10^{-1}	1.13×10^{-1}	5.23×10^{-2}	5.64×10^{-1}
h2 (SD)	3.37×10^{-3}	4.20×10^{-3}	2.12×10^{-3}	1.14×10^{-3}	4.14×10^{-3}	5.94×10^{-3}	4.63×10^{-3}	2.01×10^{-2}
nc@p9 (mean)	5.60×10^{3}	1.24×10^{4}	8.60×10^{3}	1.40×10^{4}	9.60×10^{3}	3.02×10^{3}	9.69×10^{2}	3.40×10^{3}
nc@p9 (SD)	4.00×10^{2}	1.52×10^{3}	2.00×10^{2}	5.71×10^{2}	2.00×10^{2}	8.27×10^{2}	1.06×10^{3}	3.02×10^{2}
AIC	3.08×10^{1}	1.69×10^{0}	1.68×10^{2}	1.97×10^{1}	4.10×10^{2}	3.34×10^{0}	1.72×10^{0}	2.42×10^{1}

BIP = bipolar disorder; DEP = depression; EP = all epilepsy; FEP = focal epilepsy; h2 = heritability; nc@p9 = number of causal variants with strongest effects required to explain 90% variance at genome-wide significance; pi = polygenicity; SCZ = schizophrenia; sig2_beta = discoverability.

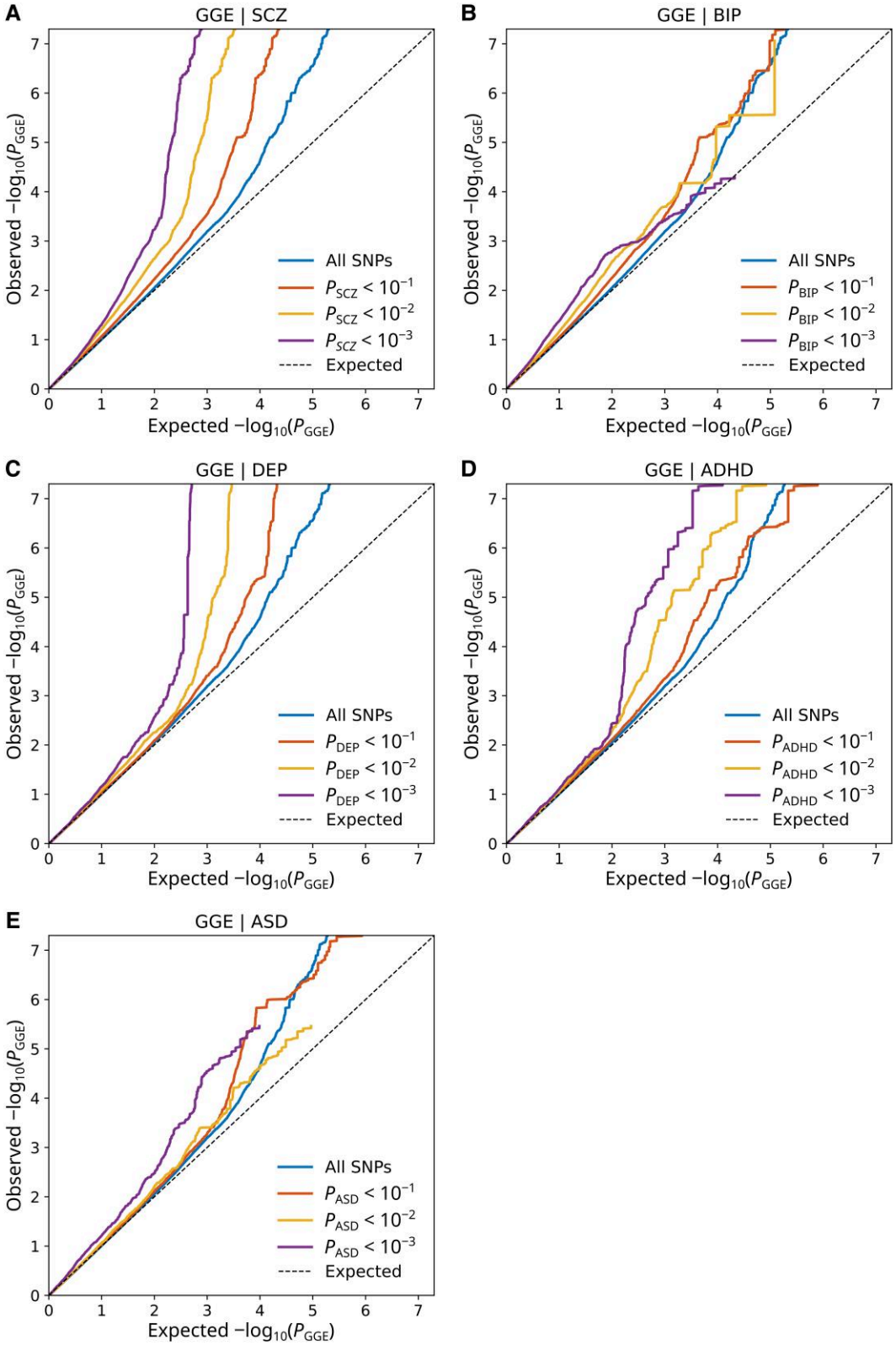

Figure 1 Cross-trait enrichment between GGE and psychiatric disorders. Quantile-quantile (Q-Q) plots show SNP enrichment for GGE conditional on SNP associations with (**A**) schizophrenia (SCZ), (**B**) bipolar disorder (BIP), (**C**) depression (DEP), (**D**) ADHD and (**E**) ASD. Conditional Q-Q plots of nominal versus empirical –log10 *P*-values (corrected for inflation) in GGE below the standard GWAS threshold of $P < 5 \times 10^{-8}$ as a function of significance of association with the psychiatric disorders, at the level of $P < 0.10$, $P < 0.01$ and $P < 0.001$. The blue lines indicate all SNPs. The dashed lines indicate the null hypothesis.

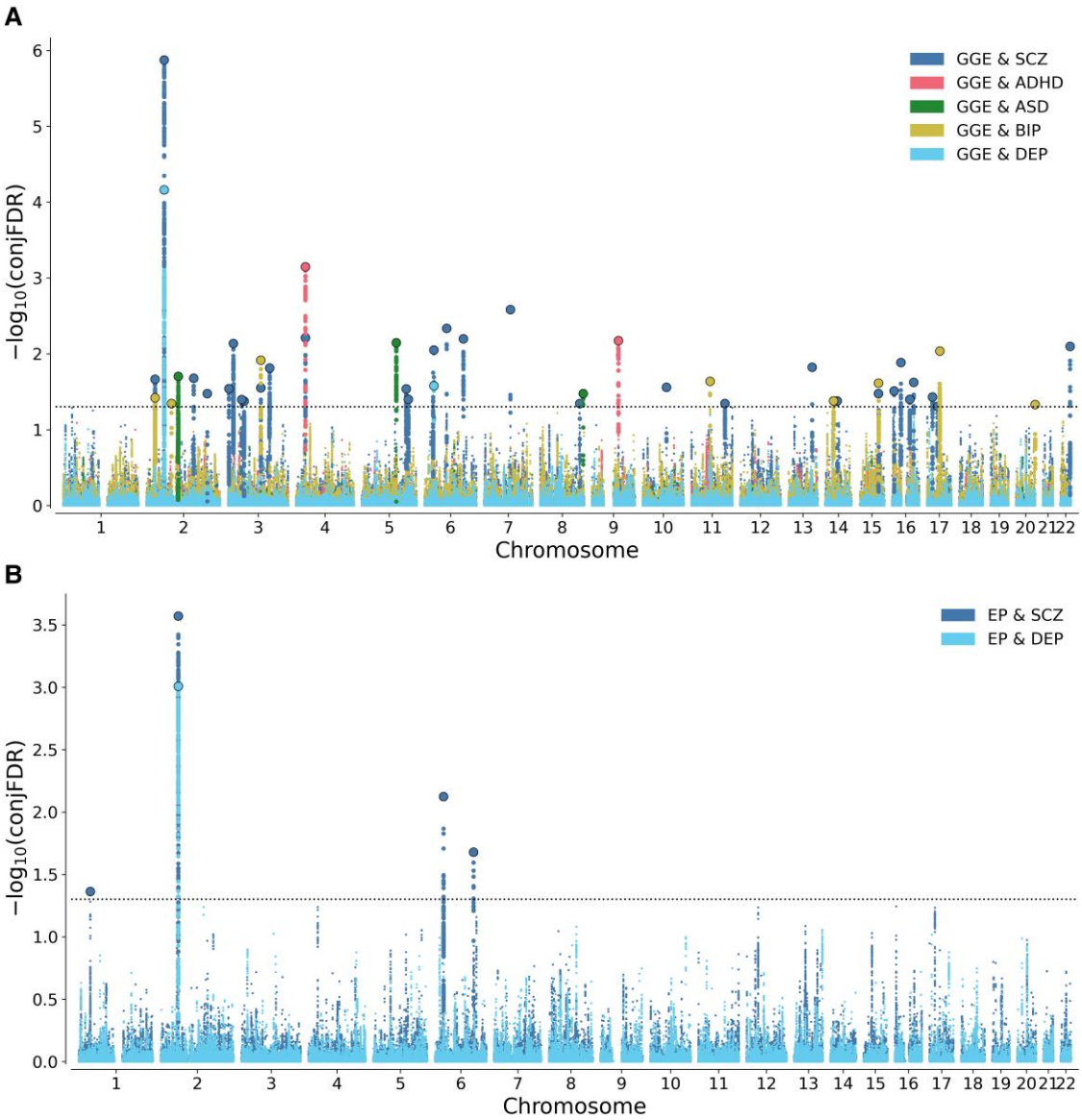

Figure 2 Shared loci between epilepsy and psychiatric disorders at conjFDR < 0.05. (**A**) Common genetic variants jointly associated with GGE and psychiatric disorders at conjFDR < 0.05. SCZ = schizophrenia; BIP = bipolar disorder; DEP = depression; Manhattan plots showing the −log10 transformed conjFDR values for each SNP on the y-axis and chromosomal positions along the x-axis. The dotted horizontal lines represent the threshold for significant shared associations [conjFDR <0.05, i.e. −log10(conjFDR) > 1.3]. Independent lead SNPs are circled in black. The significant shared signals in the MHC region are represented by one lead SNP only. For further information about the identified variants and loci, see Supplementary Tables 1–5. (**B**) Common genetic variants jointly associated with all epilepsy and schizophrenia and depression at conjFDR < 0.05. EP = all epilepsy. Manhattan plots showing the −log10 transformed conjFDR values for each SNP on the y-axis and chromosomal positions along the x-axis. The dotted horizontal lines represent the threshold for significant shared associations [conjFDR <0.05, i.e. −log10(conjFDR) > 1.3]. Independent lead SNPs are circled in black. The significant shared signals in the MHC region are represented by one lead SNP only. For further information about the identified variants and loci, see Supplementary Tables 7 and 8.

evident cross-trait enrichment between focal epilepsy and the other psychiatric disorders.

Shared loci between common epilepsies and psychiatric disorders

Next, we leveraged the bi-directional cross-trait enrichment to increase statistical power for discovery of shared loci using conjFDR analysis. At conjFDR <0.05, we identified 30 loci significantly associated with both GGE and schizophrenia, eight loci shared between GGE and bipolar disorder, two loci shared between GGE and depression, two loci shared between GGE and ADHD, and three loci shared between GGE and ASD (Fig. 2A and Supplementary Tables 1–6). Taken together, we identified a total of 39 distinct loci associated with GGE of which 32 are novel risk loci for GGE (Table 3 and Supplementary Table 6). Four of the loci were novel for psychiatric disorders; one locus on chromosome 11 at *HNRNPA1P60* for schizophrenia, two loci at chromosomes 2 (at *RN7SL201P*) and 20 (at *ZNF512B:LINC00176*) for bipolar disorder and one locus at chromosome 2 (at *AC018880.2*) for ASD (Supplementary Tables 1–5). Further, we identified four loci jointly associated with all epilepsies and

Table 3 All distinct loci associated with GGE at conjFDR < 0.05

CHR	LEAD_SNP	Nearest gene	A1/A2	P-value	Novel in epilepsy	Psychiatric disorder shared with	Concord effect
2	rs6708889	MRPL33:RBKS	T/C	6.22×10^{-5}	Novel	BIP, SCZ	Yes
2	rs1040225	VRK2	G/A	1.53×10^{-10}	ILAE 2014	SCZ, DEP	No
2	rs6715448	RN7SL201P	C/T	8.24×10^{-5}	Novel	BIP	No
2	rs1673468	AC018880.2	T/C	4.30×10^{-5}	ILAE[25]	ASD	No
2	rs249697	AC009227.3	A/G	7.90×10^{-5}	Novel	SCZ	No
2	rs6714133	SATB2:SATB2-AS1	G/T	1.60×10^{-4}	Novel	SCZ	Yes
3	rs17194427	CNTN4	C/A	1.25×10^{-4}	Novel	SCZ	Yes
3	rs10428260	TBC1D5	A/G	1.85×10^{-5}	Novel	SCZ	Yes
3	rs75298156	RP11-944L7.4:ZNF197	A/G	2.14×10^{-4}	Novel	SCZ	Yes
3	rs62256903	SMIM4	G/A	2.30×10^{-4}	Novel	SCZ	No
3	rs3804640	CD47	A/G	1.20×10^{-5}	Novel	BIP, SCZ	Yes
3	rs4678442	RP11-731C17.1	A/G	5.06×10^{-5}	Novel	SCZ	No
4	rs6448744	PCDH7	T/G	4.20×10^{-8}	ILAE 2014	ADHD, SCZ	No
5	rs434517	RP11-492A10.1	C/A	7.25×10^{-7}	ILAE[2]	ASD	No
5	rs4515335	PPP2R2B	G/A	1.27×10^{-4}	Novel	SCZ	No
5	rs815624	MFAP3	T/C	2.10×10^{-4}	Novel	SCZ	No
6	rs2260000	PRRC2A	C/T	2.40×10^{-5}	Novel	SCZ, DEP	Yes
6	rs1572208	RIMS1	T/C	1.03×10^{-5}	Novel	SCZ	Yes
6	rs7742212	PTPRK	A/G	9.10×10^{-6}	ILAE[2]	SCZ	Yes
7	rs12704290	GRM3	G/A	5.03×10^{-6}	Song *et al.*[52]	SCZ	No
8	rs7016267	FAM49B	C/T	2.60×10^{-4}	Novel	SCZ	Yes
8	rs11782665	AC138647.1	A/C	8.40×10^{-5}	Novel	ASD	Yes
9	rs13290882	KIF27	G/A	1.16×10^{-5}	ILAE[25]	ADHD	Yes
10	rs1873691	KCNMA1	G/A	1.19×10^{-4}	Novel	SCZ	No
11	rs174605	FADS2	G/T	2.87×10^{-5}	Novel	BIP	No
11	rs56186611	HNRNPA1P60	C/T	1.53×10^{-4}	Novel	SCZ	No
13	rs73550679	HS6ST3	C/T	4.17×10^{-5}	Novel	SCZ	No
14	rs12885033	MDGA2:MDGA2	A/C	7.20×10^{-5}	Novel	BIP	Yes
14	rs55643369	CTD-2315A10.2	T/C	7.56×10^{-5}	Novel	SCZ	Yes
15	rs2055891	HOMER2	A/G	3.10×10^{-5}	Novel	BIP, SCZ	No
16	rs4350587	RBFOX1	A/G	1.40×10^{-4}	ILAE[25]	SCZ	Yes
16	rs12325539	DOC2A	T/C	4.00×10^{-5}	Novel	SCZ	No
16	rs72790284	CNOT1	C/T	2.11×10^{-4}	Novel	SCZ	Yes
16	rs13333786	AC010547.9:ZNF19	T/C	9.40×10^{-5}	Novel	SCZ	Yes
17	rs8071147	PRPSAP2	G/A	1.44×10^{-4}	Novel	SCZ	Yes
17	rs2306593	MYO19	T/C	3.00×10^{-4}	Novel	SCZ	Yes
17	rs4473241	CTB-175E5.7	G/T	8.40×10^{-6}	Novel	BIP	No
20	rs3829704	ZNF512B:LINC00176	C/T	8.70×10^{-5}	Novel	BIP	No
22	rs133568	MIR3201	A/G	2.50×10^{-6}	Novel	SCZ	No

P-values are reported for the epilepsy phenotype. Detailed information about the reported loci can be found in Supplementary Tables 1–8. BIP = bipolar disorder; DEP = depression; SCZ = schizophrenia.

Table 4 All distinct loci associated with all epilepsy at conjFDR < 0.05

CHR	LEAD_SNP	Nearest gene	A1/A2	P-value	Novel in epilepsy	Psychiatric disorder shared with	Concord effect
1	rs13374459	MACF1	T/C	3.86×10^{-5}	Novel	SCZ	No
2	rs2717055	CTD-2026C7.1	A/G	5.53×10^{-7}	ILAE 2014	DEP, SCZ	No
6	rs7766356	ZSCAN23	T/C	5.76×10^{-6}	Novel	SCZ	Yes
6	rs13219424	PTPRK	C/T	2.40×10^{-5}	ILAE[2]	SCZ	Yes

P-values are reported for the epilepsy phenotype. Detailed information about the reported loci can be found in Supplementary Tables 1–8. BIP = bipolar disorder; DEP = depression; SCZ = schizophrenia.

schizophrenia, and one locus shared between all epilepsies and depression, the same that was linked to GGE (Fig. 2B and Table 4). Among these loci, the risk locus at chromosome 1 at *MACF1* and at chromosome 6 at *ZSCAN23* are novel findings for epilepsy (Supplementary Tables 7 and 8).

Next, we evaluated the effect directions of the lead variants for each shared locus (Supplementary Tables 1–8). In the schizophrenia loci shared with GGE, 15 of the 29 lead SNPs had the same allelic effect directions. In the schizophrenia loci shared with all epilepsies, one of four lead SNPs had the same allelic effect directions. In the locus shared between depression, GGE and all epilepsies, the risk for depression was linked to lower risk of epilepsy. In the bipolar disorder loci, three of the eight lead SNPs had the same allelic effect directions in GGE. In the ADHD loci, one of the two lead SNPs, and in the ASD loci, one of the three lead SNPs had the same allelic effect directions in GGE.

Functional annotation

Functional annotation of the candidate SNPs showed that the majority of the SNPs were located in intergenic and intronic regions (Supplementary Tables 9–13, 15 and 16). There was a total of 11 non-synonymous exonic variants, which were detected within the seven loci implicating the genes *VRK2*, *GNL3*, *FAM114A2*, *PRPSAP2*, *C15orf40*, *C17orf53*, *ASB16*, *KIF27* and *RMI1* (Supplementary Table 14). Among the shared loci, 84 candidate SNPs had a CADD-score higher than 12.37, which is suggested to reflect deleteriousness.[53] Using the three-way gene mapping strategy, the 40 distinct loci were linked to 560 genes (Supplementary Tables 17–23). We identified 19 gene-sets significantly enriched with the genes mapped to the loci shared between schizophrenia and GGE after correcting for multiple comparisons (Supplementary Table 24). The most strongly associated gene-sets were linked to cell cycle regulation and protein serine threonine phosphatase activity, as well as membrane and vesicle function (Supplementary Table 24). The gene-set analyses of the other groups of shared loci were underpowered. Additionally, we determined the differential gene expression of the mapped genes across human tissues (Supplementary Figs 6–19).

Sign concordance test

For GGE, 64 of 91 lead SNPs with conjFDR < 0.10 were sign concordant in the discovery and the independent samples (binomial test P-value = 6.6×10^{-5}) (Supplementary Tables 1–8). For schizophrenia, 41 of 55 lead SNPs with conjFDR < 0.10 were sign concordant (P-value = 0.001). For bipolar disorder, 17 of 22 lead SNPs with conjFDR < 0.10 were sign concordant (P-value = 0.0084). All eight lead SNPs associated with depression at conjFDR <0.10 were sign concordant (P-value = 0.0039). For ADHD, three of five lead SNPs with conjFDR < 0.10 were sign concordant (P-value = 0.5). Finally, all four lead SNPs associated with ASD at conjFDR < 0.10 had concordant effects (P-value = 0.0625).

Discussion

In the current study, we demonstrate substantial overlap in common genetic variants influencing common epilepsies and major psychiatric disorders, along with differences in their genetic architectures. First, we demonstrate that the epilepsy phenotypes were considerably less polygenic (1.0 K–3.4 K causal variants) than the psychiatric disorders (5.6 K–13.9 K causal variants; Table 2). Hence, the overlapping genomic loci represent a larger fraction of the genetic architecture underlying the epilepsies than the psychiatric disorders. Then, using the conjFDR method, we leveraged the substantial cross-trait enrichment between epilepsies and psychiatric disorders to boost statistical power. We identified a total of 39 loci shared between GGE and psychiatric disorders and four loci shared between all epilepsy and psychiatric disorders (Fig. 2A, B and Tables 3 and 4). Among the 40 distinct loci identified in total, 32 were novel GGE risk loci and two were novel for all epilepsy (Tables 3 and 4). For schizophrenia, bipolar disorder, depression and GGE, we observed a high degree of sign concordance of the identified lead variants between the discovery and independent samples, supporting the reliability of the findings, while the sign tests for the remaining phenotypes were underpowered. Altogether, the study aligns with recent GWAS analyses suggesting shared genetic risk between neurological and psychiatric disorders,[34–36] indicating that common genetic variants may jointly influence the risk of common epilepsies and psychiatric disorders and providing new insights into their shared genetic aetiology.

Most of the identified epilepsy loci (both all epilepsy and GGE) were shared with schizophrenia. The different number of loci shared with each psychiatric disorder may partly reflect the differences in GWAS sample sizes and power, with schizophrenia GWAS being considerably well powered.[19] Despite a considerable comorbidity between epilepsy and ASD[54] and rare protein-disrupting genetic variants jointly linked to these disorders,[55] we only identified three loci shared between ASD and GGE. However, this is not unexpected given the low power of the ASD GWAS.[16] Further, ASD is also one of the least discoverable traits; in comparison schizophrenia is estimated to be 2.5 times more discoverable than ASD (Table 2). Recent cross-disorder analyses of GWAS data[56] suggest substantial polygenic overlap between psychiatric disorders, and it is likely that many of the shared loci identified here will be linked to several psychiatric disorders as GWAS increase in size. The smaller genetic enrichment observed for focal epilepsy and all epilepsy is likely due to the lower SNP heritabilities (h^2 = 5% and 11%, respectively) of these epilepsy phenotypes compared to GGE (h^2 = 56%; Table 2). In line with this, MiXeR estimates that the genetic variance underlying GGE is twice more discoverable than focal epilepsy (Table 2). Taken together with polygenicity and heritability estimates, these differences in the genetic architectures of epilepsies may explain why we discovered more genetic loci associated with GGE than with focal epilepsy despite similar sample sizes. There was a mixed pattern of allelic effect directions among the shared loci, suggesting a complex genetic relationship between the disorders, in line with the bi-directional relationship between epilepsies and psychiatric disorders. This mirrors findings from other cross-trait investigations of genetic overlap in the recent years, demonstrating extensive pleiotropy of common variants with mixed effect directions among brain-related traits and disorders.[34–36] While the weak or absent genetic correlations[2,25] between epilepsy and psychiatric disorders cannot explain the comorbidity between these disorders, the present findings of mixed effects may indicate that in subgroups of patients, common genetic variants may increase susceptibility of both epileptic seizures and mental illness. Further research is needed to evaluate whether genomic prediction tools may help pinpoint individuals at higher risk of such comorbidity. Despite the discovery of many novel loci, these loci only represent a minor fraction of the total genetic risk architectures underlying these disorders, which involve thousands of common genetic variants (Table 2). To achieve clinically meaningful prediction of genomic prediction tools it is necessary to identify a considerably larger proportion of the common variants explaining variation in risk of these disorders.[57,58] Hence, it is important to continue the efforts to assemble large-scale GWAS on diverse, well phenotyped populations to enable clinical translation of the emerging genomic findings.

Among the identified loci, five (at genes *MRPL33:RBKS*, *VRK2*, *CD47*, *PRRC2A*, *PCDH7* and *HOMER2*) were shared between GGE and more than one psychiatric disorder, and three (at genes *VRK2*, *ZSCAN23* and *PTPRK*) were associated with both GGE and all epilepsy phenotypes (Tables 3 and 4), indicating considerable cross-disorder effects of these loci. In total, we identified 33 novel epilepsy risk loci. Three of the identified loci (near *AC018880.2*, *KIF27* and *RBFOX1*) were not reported in the original epilepsy GWAS,[2] but reached genome-wide significance in the most recent ILAE GWAS,[25] which has not yet been peer-reviewed. Similarly, two of the loci (near *PCDH7* and *KIF27*) jointly associated with ADHD and GGE were recently reported in another study.[26] We

also detected a GGE risk locus at the metabotropic glutamate receptor *GRM3* shared with schizophrenia, which was not identified in the original ILAE epilepsy GWAS[2] but was detected in another GWAS on epilepsy,[52] supporting the validity of this finding. Moreover, the novel risk locus for all epilepsy cases at *MACF1* was previously found to be enriched for rare exonic variants in patients with epileptic encephalopathies.[59] We also detected a novel locus for all epilepsy and GGE within the extended MHC region (Tables 3 and 4). In our analysis, this locus was shared between GGE, schizophrenia and depression, as well as between all epilepsy and schizophrenia; and have previously been associated with both schizophrenia and depression.[20,21,60,61] Genetic variants within the MHC region are linked to both the innate immune system and synaptic maturation during brain development.[62] Given the long-range complex LD in the MHC region, which spans numerous genes,[63] we consider this finding to reflect the joint involvement of MHC region in these disorders, rather than any specific locus or gene, warranting further studies to disentangle the underlying genetic signal.

We linked all candidate SNPs in the loci to genes using the three-way gene-mapping procedure implemented in FUMA.[46] However, functional validation is required to determine if the implicated genes play a role in the aetiology of epilepsy and psychiatric disorders. The genes should instead be considered as starting points for generating hypotheses that can be functionally tested. For instance, among the epilepsy risk loci, there were several potassium channel genes (e.g. *KCNMA1*, *KCNJ3*, *KCNH8*, *KCNQ5*, *KCNN2*), which could be prioritized for functional follow-up experiments. Potassium channels play key roles in neuronal excitability and have previously been linked to epilepsy pathogenesis,[64–66] possibly representing novel treatment targets. Within the shared loci, we detected 11 non-synonymous exonic variants (Supplementary Table 14), which provide more direct mechanistic hypotheses since they may impact the phenotype directly by disrupting protein function or structure. The implicated genes were *VRK2*, *GNL3*, *FAM114A2*, *PRPSAP2*, *C15orf40*, *C17orf53*, *ASB16*, *KIF27* and *RMI1*; all of which seem to be involved in various metabolic processes and many are linked to signal transduction.[67–76] Nine of the non-synonymous exonic variant associations were novel for GGE, except the variants within *KIF27* and *RMI1*.[25] However, like in other GWAS,[77] most of the detected genetic variants were located in non-coding regions, indicating regulatory effects on gene expression, complicating biological interpretation. Nineteen gene-sets were significantly enriched with the genes mapped to the loci shared between schizophrenia and GGE (Supplementary Table 24). Many of these gene-sets implicated pathways related to cell cycle and phosphatase activity, particularly serine/threonine-specific phosphatases, as well as membrane and vesicle function, which play important roles in neurotransmitter support and synaptic transmission.[78,79] Of note, we did not perform gene mapping of candidate SNPs in the regions with complex long-range LD (the MHC region, 8p23.1 region and the *MAPT* region). These broad regions involve hundreds of candidate SNPs and a vast number of genes, which could be involved. However, their inclusion in the functional analysis would considerably bias these analyses.

There are some limitations to our study. Like standard GWAS, the conjFDR method detects SNP associations, but it is agnostic about the causal variant underlying the genetic signal, since multiple SNPs may be in LD with the lead SNP. Hence, we cannot exclude the possibility that the overlapping loci reflect separate causal variants.[80] Within each locus, we nevertheless identified and functionally characterized the candidate SNPs with the highest probability of being a causal variant, to allow further inspection of plausible causal variants that can be selected for experimental follow-up studies. It is likely that some of the cases in the investigated GWAS on epilepsy and psychiatric disorders had or may develop comorbid mental illness or epilepsy, which might bias our investigation of genetic overlap. However, this potential bias cannot explain the presence of mixed effect directions among the shared loci. Another limitation was the focus on individuals of European ancestry. Participants in the discovery samples were predominantly of European ancestry to ensure compatibility in LD patterns, which might otherwise bias the conjFDR analyses. However, the high degree of sign consistency observed in the validation schizophrenia GWAS in East Asian individuals[19] suggests that the findings are also generalizable to this population. Improving the diversity in GWAS populations remains a key issue for the genomics research.[81]

In conclusion, we demonstrate extensive polygenic overlap between common epilepsies and major psychiatric disorders and identified 40 shared risk loci with mixed effect directions, 32 of which are novel loci for GGE, two novel loci associated with all epilepsy phenotypes and four novel loci for psychiatric disorders. As GWAS get larger, we expect that many more loci will be found to jointly influence epilepsy and psychiatric disorders, which may eventually inform clinical practice.

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Competing interests

O.A.A. has received speaker's honorarium from Lundbeck and is a consultant for Healthlytix. 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. Remaining authors have no conflicts of interest to declare.

Supplementary material

Supplementary material is available at *Brain* online.

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