


Genome-wide association analysis links multiple psychiatric liability genes to oscillatory brain activity

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Abstract

Oscillatory activity is crucial for information processing in the brain, and has a long history as a biomarker for psychopathology. Variation in oscillatory activity is highly heritable, but current understanding of specific genetic influences remains limited. We performed the largest genome-wide association study to date of oscillatory power during eyes-closed resting electroencephalogram (EEG) across a range of frequencies (delta 1–3.75 Hz, theta 4–7.75 Hz, alpha 8–12.75 Hz, and beta 13–30 Hz) in 8,425 subjects. Additionally, we performed KGG positional gene-based analysis and brain-expression analyses. *GABRA2*—a known genetic marker for alcohol use disorder and epilepsy—significantly affected beta power, consistent with the known relation between $GABA_A$ interneuron activity and beta oscillations. Tissue-specific SNP-based imputation of gene-expression levels based on the GTEx database revealed that hippocampal *GABRA2* expression may mediate this effect. Twenty-four genes at 3p21.1 were significant for alpha power (FDR $q < .05$). SNPs in this region were linked to expression of *GLYCK* in hippocampal tissue, and *GNL3* and *ITIH4* in the frontal cortex—genes that were previously implicated in schizophrenia and bipolar disorder. In sum, we identified several novel genetic variants associated with oscillatory brain activity; furthermore, we replicated and advanced understanding of previously known genes associated with psychopathology (i.e., schizophrenia and alcohol use disorders). Importantly, these psychopathological liability genes affect brain functioning, linking the genes' expression to specific cortical/subcortical brain regions.

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KEYWORDS

brain expression pathway, electroencephalography (EEG), endophenotype, genetic correlation, Genome-Wide Association Study (GWAS), SNP heritability

1 | INTRODUCTION

Oscillations in neuronal activity are known to play a crucial role in information processing and cortical communication (Başar, 2012; Buzsáki, 2006; Cardin et al., 2009; Cho et al., 2015; Jokisch, & Jensen, 2007; and Marín, 2012; Pandey et al., 2016; Uhlhaas, & Singer, 2010). Oscillations of different frequencies are thought to subserve different roles in neural processing. The dominant alpha oscillations (8–10 Hz) reflect the inhibition of cortical structures that are not needed for the task at hand (Jensen & Mazaheri, 2010; Mazaheri et al., 2014), whereas beta band oscillations (~20 Hz) may reflect a “hold” function, delaying behavior when beta oscillations are present. For example, beta oscillations measured in human subthalamic nucleus during deep-brain electrode implantations for the treatment of Parkinson’s Disease have a movement-prohibitive role (Engel & Fries, 2010). Recently, a more causal involvement of oscillations in driving behavior was shown (Cho et al., 2015). In this study, restoring oscillatory activity via optogenetic driving of GABA interneurons at gamma frequencies resulted in normal behavioral flexibility in *Dlx5/6+/-* transgenic mice that are otherwise affected in both frontal cortical oscillations as well as behavioral flexibility.

These findings suggest that oscillations are not just biomarkers of, but essential components in neural communication and computation. Arguably, aberrant brain oscillations will result in deviant behavior. Brain oscillations have therefore been widely investigated in the context of psychopathology—including neuropsychiatric disorders—and variation in normal human behavior (Başar & Güntekin, 2008; Skosnik, Cortes-Briones, & Hajós, 2016). This includes alpha oscillations related to intelligence (Doppelmayr et al., 2002; Thatcher, North, & Biver, 2007), slow oscillations (4–8 Hz theta and 1–4 Hz delta oscillations) in schizophrenia (Boutros et al., 2008; Sponheim, Clementz, Iacono, & Beiser, 1994), theta and beta oscillations in attentional deficits (Clarke et al., 1998; Snyder & Hall, 2006), and beta oscillations in substance use (Rangaswamy et al., 2002; Struve, Straumanis, Patrick, & Price, 1989).

As one of the most heritable traits in humans (Anokhin et al., 2001; Smit, Posthuma, Boomsma, & Geus, 2005; Smit et al., 2006; Tang et al., 2007; Van Beijsterveldt, Molenaar, De Geus, & Boomsma, 1996; Zietsch et al., 2007), EEG oscillations may serve as an intermediate phenotype in the pathway from genes to behavior (de Geus, 2010; Gottesman, & Gould, 2003; Loo et al., 2015). Despite the numerous twin and family studies of the genetics of oscillations, studies linking

specific genetic variants such as Single Nucleotide Polymorphisms (SNPs) to oscillation strength remain scarce. The first genome-wide association study of EEG oscillation strength showed an association between *SGIP1* and theta oscillations in both Native American and European Ancestry samples. Two recent studies from the Collaborative Study on the Genetics of Alcoholism (COGA) associated several inter-genetic SNPs at 6q22 in a European sample (Meyers et al., 2017a), and at 3q26 in African American ancestry (Meyers et al., 2017b) for >20 Hz fast beta oscillations.

Contrasting with these results, the largest study of EEG power and peak frequency to date (Malone et al., 2014) did not yield genome-wide significant hits. They did report, however, significant contribution of common SNP variants to the heritability using random-effects modeling (Yang et al., 2010). This suggests that statistical power to detect genome-wide significant effects is limited, as the effects of single genetic variants on complex, multifactorial phenotypes such as brain activity are expected to be very small. Therefore, our first aim was to extend previous studies by performing a meta-analysis of genome-wide association studies (GWAS) of oscillatory power across standard frequency bands, yielding the largest EEG GWAS study to date. To further understand these findings, we also estimated SNP-based heritability using LD score regression (Bulik-Sullivan et al., 2015b).

Possibly equally important is the functional annotation of GWAS results by aggregating results and/or prioritizing SNPs based on recent advances in bioinformatics and molecular knowledge of the genome. This was performed by several means. SNP-based GWAS results were followed up with gene-based analyses and expression-based enrichment analyses, which further increases power to detect genes affecting functional brain activity (Neale & Sham, 2004; Ripke et al., 2014; Watanabe, Taskesen, Bochoven, & Posthuma, 2017). In addition, significant results from gene-based tests were compared to known liability genes for behavioral phenotypes including neuropsychiatric disorders by searching GWAS results databases (ensembl.org, gwascentral.org). We opted for this method of operation—that is, a full genome scan for genetic variants, subsequent gene-based analyses, matching against known GWAS results for psychiatric/behavioral phenotypes—rather than preselecting liability genes to analyze for three reasons. First, candidate gene associations have proven much less successful in the past than genome-wide scans, even with severe adjustments for multiple testing in the latter. Second, genome-wide scans allow for the calculation of summed statistics such as SNP coheritability between EEG and behavioral traits, without the need to preselect on genome-wide

TABLE 1 Cohort summary

Abbreviation	Study cohort name	Cohort type	Ages (years)	N _{subjects}	N _{families}
NTR	Netherlands Twin Registry	Population based EUR ancestry	5.2–70.9	834 (55.5% F)	423
COGA-EA	COGA European Ancestry study	Alcohol dependent probands + pedigree EUR Ancestry	7.07–73.08	1492 (52.5% F)	117
COGA-CC	COGA Case-Control study	Alcohol dependent cases and Healthy controls (unrelated)	13.8–69.8	660 (48.3% F)	–
MTFS	Minnesota Twin Family Study	Population based EUR ancestry	17–60	4026 (48.9% F)	1612
QIMR	Brisbane Adolescent Twin Study (BATS)	Population based EUR ancestry	15.5–20.1	971 (51.3% F)	468

significant effects. Third, a GWAS of EEG traits can be used for comparison by future studies.

We then investigated enrichment for expression Quantitative Trait Loci (eQTL) that have been shown to alter expression of specific genes. These results allowed for the identification of likely target genes. These links are based on empirical associations between SNPs and gene expression rather than the clustering of SNPs based on genomic locations. This provides an important step in reducing the number of likely target genes affecting the investigated trait. Finally, we analyzed enrichment of significant genes in the available cerebral brain tissues of the GTEx database (Lonsdale et al., 2013). Using the same database, we examined how specific genes are expressed in specific brain tissues, further elucidating the pathway from genetic variation to brain activity.

In linkage and candidate gene studies, the most consistent finding has been the involvement of GABA functioning in ~20 Hz beta oscillatory activity. Porjesz et al. (2002) showed significant linkage between beta oscillations on chromosome 4 and the *GABRB1* microsatellite marker, which was overlying a cluster of GABA_A receptor genes: *GABRG1*, *GABRA2*, *GABRA4*, and *GABRB1*. Regional SNP association analysis subsequently pointed to SNPs intronic to *GABRA2* as accounting for the signal (Edenberg et al., 2004). *GABRA2* was subsequently associated with both beta oscillations and alcohol use disorders (Edenberg et al., 2004; Lydall et al., 2011). Our second aim is to replicate these findings and to investigate how genetic variation in *GABRA2* affects expression in brain tissue.

The current study describes results from the EEG workgroup of the ENIGMA consortium (Thompson et al., 2014; Thompson et al., 2017). We developed EEG processing protocols to extract common measures for band power in standard frequency bands: delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz) and beta (13–30 Hz) power at the vertex (Cz) electrode, and occipital (O1, O2) alpha power and alpha peak frequency consistent with (Malone et al., 2014). GWAS results of three population-based twin and two (alcohol-dependence) ascertained family cohorts from the Netherlands, Australia, and US were combined in a meta-analysis for a total of 8,425 individuals (see also Thompson et al., 2017). The combined meta-analyzed results were subsequently entered into the post-GWAS pipeline of analyses. Given the importance of oscillatory activity in neural communication and the large body of literature on deviant oscillatory activity in psychiatric traits, we expect that genes identified in this study will also affect neuropsychiatric and behavioral phenotypes. The subsequent expression analyses will

indicate via which pathways these genes may influence brain expression, and in turn, EEG oscillations.

2 | METHODS

2.1 | Subjects

Resting state EEG and genome-wide genotyping were available for a total of 8,425 individuals from Australia, the Netherlands, and the USA. All subjects were part of twin and family studies examining the genetics of health, neuropsychiatric and behavioral traits with additional psychophysiological assessments: the Minnesota Twin Family Study (MTFS), the Collaborative Study on the Genetics of Alcoholism (COGA), the Brisbane Adolescent Twin Study (BATS), and the Netherlands Twin Register (NTR). All sites excluded subjects with a history of neurological problems, including tumor and head trauma. Alcohol dependence ascertained samples (COGA European Ancestry Families and COGA Case-Control) required acute alcohol screening prior to EEG recording. Table 1 provides a short summary of each cohort analyzed separately before meta-analysis.

Although the age range of this sample was quite large, it is known that individual differences relative to age-group averages are moderately to highly stable, even over longer periods (Gasser et al., 1985; Smit et al., 2005). In order to maximize sample size, subjects were not excluded. However, age was carefully corrected for by including age group and/or age and age² as covariates. As a consequence, all SNP effects in this study will mostly reflect the genetic effects that are stable across the lifespan. Full details on covariates and demographics for each cohort are given in the Supporting Information Methods.

2.2 | EEG recording and preprocessing

For further details on EEG assessment by the individual groups, see supplementary material. Recording methods differed between the five included cohorts on sampling frequency, causal filter settings, and reference electrode (for COGA cohorts). Although these settings are likely to affect the recorded power values, they are also very unlikely to affect the rank ordering of power values between subjects. Since cohorts were meta-analyzed using p-values rather than inverse variance, these effects were automatically discarded, and therefore limiting concern regarding the heterogeneity introduced by recording differences across cohorts.

2.3 | EEG power and peak frequency analysis

All groups analyzed the vertex recordings (Cz) and the average of Occipital leads (O1, O2) in standard frequency bands. Cleaned data were imported into MATLAB, epoched into 2 s epochs, and power spectra calculated using Fast Fourier Transformation (FFT). Frequency bins were defined as delta (1–3.75 Hz), theta (4–7.75 Hz), alpha (8–12.75 Hz), and beta (13–30 Hz). Power was defined as the squared radius of the orthogonal sine and cosine amplitudes averaged over window size, and the mean value taken for the frequency band to obtain power density. Power values were log transformed to obtain approximate normality. Alpha peak frequency was determined using the power-weighted method in accordance with (Malone et al., 2014) between 7 and 14 Hz.

2.4 | QC and genome-wide association analysis

Groups used dosage based imputed SNP sets using CEU reference panels hg19/build 37 from 1000 genomes phase1 or phase3. Imputation followed ENIGMA imputation protocols (Thompson et al., 2014; http://enigma.usc.edu/wp-content/uploads/2012/07/ENIGMA2_1KGP_cookbook_v3.pdf). Association analyses accounted for family relatedness using various validated modeling techniques (Merlin, GEE, RFGLS). Sex, Age and age² and/or age-group/wave were used as covariates plus ancestry Principal Components plus disease status (when applicable). See supplementary materials for more group specific methods and/or deviance from these standard analyses protocols, and covariate analysis results.

Pre-meta-analysis QC were performed using EasyQC (Winkler et al., 2014). We filtered on sample MAF (0.03 for the largest dataset, MTF5; 0.04 for the intermediate datasets, COGA case control and QIMR BATS; and 0.05 for NTR and COGA EA), as well as EUR 1000 Genomes reference set MAF < 0.03, $N < 200$, HWE $p < 10^{-7}$, INFO < 0.8, INFO > 1.05, imputation $R^2 < .4$, invalid numbers (Inf, NA), 0.2 difference between sample and reference set allele frequencies. Further checks consisted of matching alleles, duplicates, and strand flips. Meta-analyzed SNPs were filtered for combined $N > 6,000$. The final datasets consisted of 4959085 to 4959521 SNPs depending on phenotype. Supporting Information Table shows the number of SNPs lost at each QC step for Cz alpha. Genome-wide significance was set at 5×10^{-8} .

2.5 | SNP heritability

LD score regression (Bulik-Sullivan et al., 2015b) uses the natural experiment present in the genome due to variable amounts of Linkage Disequilibrium (LD) between SNPs. Causal variants will cause straight slope decline in test statistics of nearby SNPs with decreasing levels of LD to the causal variant in the case of additive genetic variation. The slope of the regression line of the chi-square statistic against LD scores across the genome reflects the heritability of the trait (Bulik-Sullivan et al., 2015b). SNP heritability estimation using LD score regression has the advantage of being insensitive to population stratification effects, as these will result in an upward shift across all LD score bins, thus

affecting the intercept and not the slope of the LD-dependent regression.

We used LD score regression to estimate the SNP-based heritability of the six EEG phenotypes following the recommendations in Bulik-Sullivan et al. (2015b), including pruning for Hapmap 3 SNPs. Next, the LD-score regression intercept was used to assess quality of the GWAS and removal of stratification effects by the population Principal Components (see for example Okbay et al., 2016a). Finally, we used bivariate LD-score regression to estimate genetic correlation r_G , between the EEG phenotypes and GWASs available in LD Hub (<http://ldsc.broadinstitute.org>) (Bulik-Sullivan et al., 2015a; Zheng et al., 2017). This includes GWASs on schizophrenia and alcohol use disorders. We additionally examined bipolar disorder, subjective wellbeing, neuroticism, generalized epilepsy and educational attainment (ILAE Consortium, 2014; Okbay et al., 2016b), to explore the genetic association of oscillatory activity with these behavioral and neurological traits. Finally, we investigated genetic correlations between our EEG GWAS results and the ENIGMA GWAS results for subcortical volumes, intracranial volume, and brain volume. See Supporting Information Methods for a full reference list.

3 | RESULTS

3.1 | Genome-wide association

Supporting Information Figure S1 shows the Manhattan plots for the six EEG traits. Two SNPs reached genome-wide significance ($p < 5 \times 10^{-8}$), for Cz alpha power: (rs984924, $p = 4.7 \times 10^{-8}$ and rs10231372, $p = 2.9 \times 10^{-8}$); rs984924 on chromosome 4 is an intronic variant within protein kinase cGMP-dependent Type II (PRKG2), and rs10231372 on chromosome 7 is an intronic variant within the long non-coding RNA gene *LINC00996*. Suggestive peaks ($p < 5 \times 10^{-7}$) were found for Cz delta power on chromosome 5 (rs6867021, $p = 1.1 \times 10^{-7}$), chromosome 6 (rs17055223, $p = 3.1 \times 10^{-7}$), chromosome 2 (rs11677128, $p = 4.3 \times 10^{-7}$); Cz alpha power on chromosome 1 (rs10910665, $p = 1.8 \times 10^{-7}$) and on chromosome 13 (rs9514041, $p = 1.4 \times 10^{-7}$). Supporting Information Table S1 shows the genome-wide significant SNPs, suggestive peaks, and FDR significant discoveries. Note that no individual SNP effects showed significant heterogeneity I^2 , (nominal $p > .38$); however, these heterogeneity estimates are not best suited for a small number of cohorts (von Hippel, 2015).

Q-Q plots for the meta-analysis are provided in Figure 1 (pink dots). Full genome median lambdas ranged from 1.02 to 1.06. To test for inflation, we calculated LD-score regression intercepts. These were not significant for delta, theta, and alpha oscillations and alpha peak frequency ($abs(z) < 1.50$); however, beta power did show significant inflation ($z = 2.1$). Correction of beta oscillation GWAS p -values using the intercept had only minor effect and did not change any SNP or gene-based results. Overall, LD score intercept results indicated that there is no evidence of substantial inflation of statistics due to, for example, residual population stratification effects.

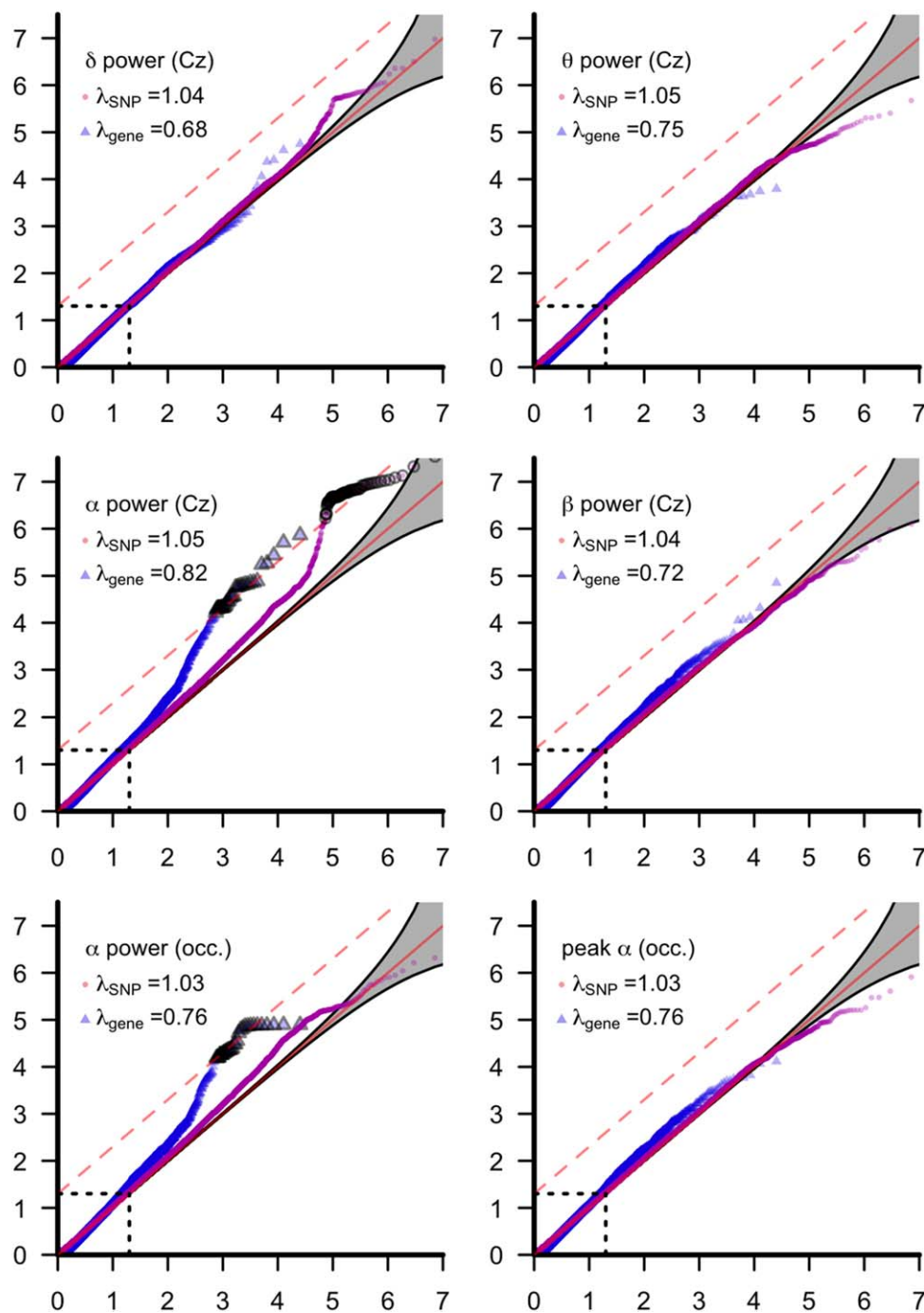


FIGURE 1 Quantile-quantile plots of observed versus expected $-\log_{10}(p)$ for delta, theta, alpha, and beta EEG power at the vertex, occipital alpha power, and occipital alpha peak frequency. Red line is the expected null, grey area is the 95% confidence interval. Dashed red line is the Benjamini-Hochberg FDR $q = .05$ threshold. Pink dots are meta-analyzed SNP p values. FDR-corrected significance is reached for alpha power at Cz. Blue triangles are KGG gene-based test p values combining SNP effects within gene regions plus 50k base pairs 3' and 5' UTR. Many genes reach FDR significance for alpha oscillation power (see Supporting Information Table S2) [Color figure can be viewed at wileyonlinelibrary.com]

3.2 | Positional gene-based analysis

We performed gene-based analysis using KGG Extended Simes test for each of the EEG traits, which combined the SNP p -values within genes plus flanking regions 50k basepair extensions in 5' and 3' UTR directions while taking into account the LD structure. Q-Q plots are included in Figure 1 (blue triangles). Plots showed inflation for gene p -values

compared to SNP p -values. Figure 2 shows the gene-based Manhattan plots. FDR-corrected p -values showed significant genes for delta, theta, and alpha power at the vertex. Supporting Information Table S2 shows the statistically significant gene discoveries (FDR $q = .05$).

Consistent with the SNP-based findings, *PRKG2* was significant for Cz alpha power ($p = .019$). In addition, *LOC101928942* reached

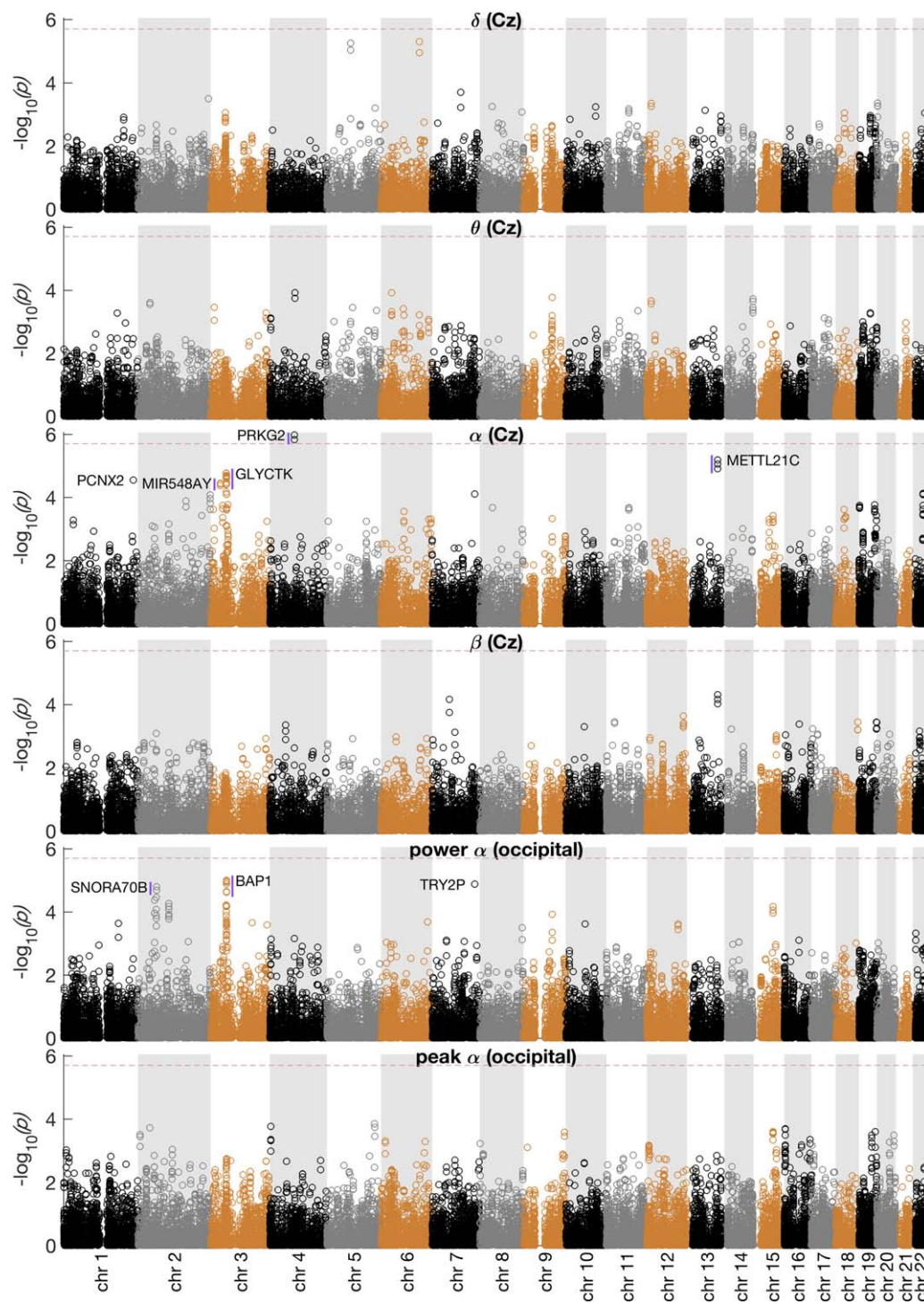


FIGURE 2 KGG gene-based test results Manhattan plots for the six EEG traits measured at the vertex electrode (Cz) and occipital (O1/O2). Dashed line is the threshold for genome-wide significance. Named genes are significant discoveries under FDR $q = .05$. Only peak findings in the significant region marked with blue vertical lines are shown. A full listing of FDR significant genes is provided in Supporting Information Table S2 [Color figure can be viewed at wileyonlinelibrary.com]

significance ($p < .019$). This gene is an antisense noncoding RNA gene embedded in *PRKG2*. Both Cz and occipital alpha power showed a cluster of significant genes at 3p21 ranging from (hg19) basepair positions 52234203 to 52728499 (*ALAS1* to *GLT8D1*). For Cz alpha power, 17 of these genes were significant discoveries at $q = .05$. For occipital alpha power, 11 genes reached significance of which 4 overlapped

with Cz alpha. Supporting Information Figure S2 (top) shows the regional Cz alpha LocusZoom plot of the chromosome 3 region revealing high LD from about 52.2–52.8 Mb (hg19). Variants within the same region have been consistently associated with schizophrenia and bipolar disorder (Ripke et al., 2013; Sklar et al., 2011). Supporting Information Figure S2 (bottom) shows the regional association plot for the

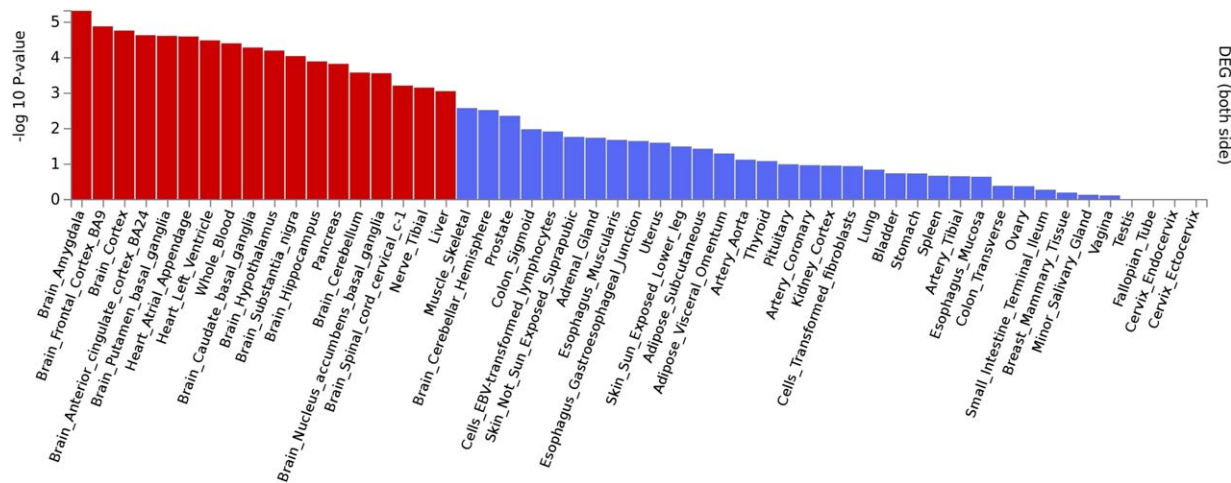


FIGURE 3 FUMA (Watanabe et al., 2017) enrichment analysis. The top 500 genes in the occipital alpha analysis are significantly enriched for genes that are up or down regulated in all cortical and subcortical brain tissues from the GTEx database, save cerebellar hemisphere. Other significantly enriched tissues are heart, whole blood, pancreas, tibial nerve, and liver [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1002/1hbm2.4238)]

second Psychiatric Genomics Consortium schizophrenia GWAS (Ripke et al., 2014) for comparison. Top SNP in this region was rs7614727 ($p = 2.0 \times 10^{-6}$), which is intronic to *WDR82*—previously associated with bipolar disorder and schizophrenia.

Further significant findings include a cluster of three genes (*METTL21C*, *TPP2*, and *CCDC168*; FDR $p = .033$ for all) for Cz alpha power. Of these, *METTL21C* has previously been associated to alpha oscillation strength (Malone et al., 2014).

3.3 | eQTL expression analysis

To investigate which genes are likely to mediate phenotypic variation in high LD regions and to elucidate mediating brain tissue expression pathways, we performed eQTL analysis. A substantial percentage of eQTLs affect the expression of genes at a distance, often including variants close to a different gene in a different LD region (Ramasamy et al., 2014). Cis-eQTLs are genetic variants within a 1 Mb region of a gene that explain variability in the expression of the gene in a target tissue (Gamazon et al., 2013; Gamazon et al., 2015; Lonsdale et al., 2013). We selected eQTLs from eight brain tissues from the GTEx database (Lonsdale et al., 2013). Cz alpha power associated p-values resulted in inflated Q-Q plots for all tissues (Supporting Information Figure S3). Benjamini-Hochberg FDR significant effects at $q = .05$ were observed for the Frontal Cortex and Anterior Cingulate Gyrus, and the Hypothalamus. Occipital alpha power showed similar effects, but for different brain regions (Caudate, Nucleus Accumbens, Hippocampus; Supporting Information Figure S4). The significant SNPs were frontal cortical tissue eQTLs for *MTERF4*, *GNL3*, and *ITIH4*; the latter two being schizophrenia/bipolar disorder liability genes at 3p21. Significant SNPs for occipital power were cortical-tissue eQTLs for genes *IL1RL1*, *IL18R1*, *CLHC1*, *GLYCTK*, and *ITIH4*. Supporting Information Table S3 lists the eQTL effects.

To test for overall significance of gene-expression enrichment in alpha oscillation power, we used the online tool FUMA (Watanabe et al., 2017). We extracted the top 500 genes from the gene-based

association (Cz and occipital alpha), which were matched against genes significantly up- or downregulated in each GTEx tissue compared to the average of other tissues (i.e., differentially expressed genes determined by a Bonferroni-corrected t test). Significance of enrichment was determined by the hypergeometric test with Bonferroni correction. Figure 3 shows that brain derived tissues are almost invariably significant, and much more so than other tissues. Other tissues—less clearly related to brain oscillations—also show significant enrichment (heart, whole blood, pancreas, tibial nerve, and liver). This is largely attributed to pleiotropy. However, causal effects and spurious relations cannot be excluded.

3.4 | Imputed gene-expression association of alpha oscillations

To further elucidate the tissue-expression pathways of the specific genes implicated in the eQTL analysis (*MTERF4*, *GNL3*, *ITIH4*, *IL1RL1*, *IL18R1*, *CLHC1*, *GLYCTK*, and *ITIH4*) we applied MetaXcan using the all GTEx cortical brain tissues (Barbeira et al., 2016; Gamazon et al., 2015). MetaXcan may have increased power to detect significant gene/phenotype associations by combining genetic variants in a sparse elastic net prediction model rather than focusing on association results from single SNPs (eQTLs). All genes, excluding *CLHC1*, reached significance in at least one tissue. Four genes near the 3p21 region showed at least one FDR significant association (*ITIH4*, *GNL3*, *GLYCTK*, and *TEX264* as an additional gene within the region). Figure 4 shows the $-\log_{10}(p\text{-value})$ for all genes with FDR significant effects in at least one tissue (indicated by the dot). *ITIH4* showed a more widespread association across tissues (significant in hypothalamus), whereas *GLYCTK* showed a rather specific hippocampal expression for both occipital and Cz alpha power. Immune genes *IL1RL1* and *IL18R1* on chromosome 2 also reached the threshold for significance in the significant association with cortical and subcortical expression with alpha oscillations (see Figure 4). Note that the positional gene-based test pointed to *MTERF4* expression in the putamen reached significance for Cz alpha power.

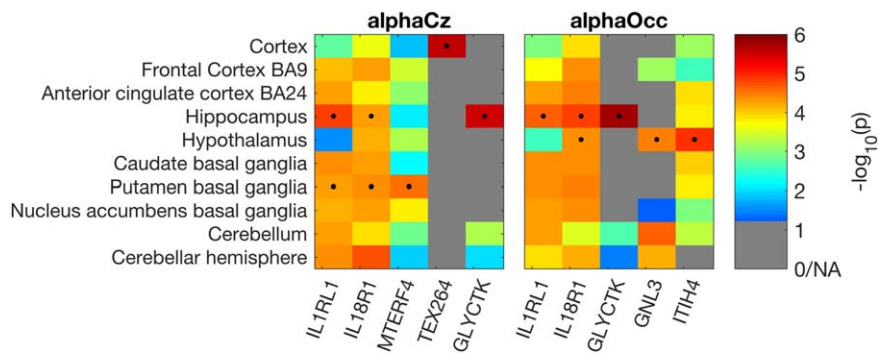


FIGURE 4 MetaXcan gene-expression results for chromosomes 2 and 3 indicate which positional gene-based discoveries and which brain tissues may be involved in affecting alpha oscillation power. Uncorrected p-values are shown, FDR significant discoveries are marked with a dot. Out of the 24 significant genes in region 3p21, *GLYCTK* associated with alpha power via hippocampal expression, *TEX264* via general cortical expression, *GNL3* and *ITIH4* via hypothalamic expression. Furthermore, *IL18R1*, *IL1RL1*, and *MTERF4* on chromosome 2 were not discovered in the positional analysis. These genes affected alpha oscillations via the Putamen and Hippocampus, but *IL1RL1* and *IL18R1* expression in many other tissues just failed to reach the FDR threshold. Note that FDR correction was performed within tissue [Color figure can be viewed at wileyonlinelibrary.com]

3.5 | GABA_A receptor genes

Planned comparisons for two GABA_A receptor genes at 4p12 were made in relation to beta power. The results from the KGG GATES positional gene-based analysis showed significant results for *GABRA2* ($p = .024$) and *GABRB1* ($p = .15$). After removing the results from the COGA sample—on which the previous findings were based—the p value increased to $p = .052$ for *GABRA2*, just missing the .05 mark. MetaXcan analysis, however, showed that imputed hippocampal expression of *GABRA2* was significantly associated with beta power for hippocampal expression of *GABRA2* ($p = .0024$). This effect remained significant after removal of the COGA samples ($p = .0050$). *GABRA2* expression in other tissues was not significantly associated with beta power ($p > .2$).

3.6 | SNP-based heritability

LD score regression for Hapmap 3 annotated SNPs ($N_{\text{SNP}} > 819\text{k}$) was carried out for SNP effects from the meta-analysis. Heritability estimates (ranging from 0.11 to 0.27; Supporting Information Figure S5) were lower than estimates from twin and family studies of EEG power (ranging from 0.45 to 0.9; e.g., see Smit et al., 2005), but are in line with the GCTA random-effects modeling on common SNPs for the same EEG measures (Malone et al., 2014), as well as other neuropsychiatric and behavioral traits.

3.7 | Genetic correlation analysis

Bivariate LD score regression was used to calculate genetic correlation r_G between traits. Supporting Information Figure S6 shows the genetic correlations between the EEG phenotypes. Strong and positive genetic correlations were observed among the EEG power phenotypes. Occipital and Cz alpha power correlated 1.0 ($p < 1\text{E-}80$), and correlated highly with Cz beta power ($r_G = .67$, $p < 3.3\text{E-}5$; and $r_G = .71$, $p < 2.8\text{E-}9$ respectively). Slow oscillatory power (delta and theta) also correlated near 1.0 ($p < 1\text{E-}20$). Only the theta with beta power genetic correlation was modest and not statistically significant

($p = .16$). Negative correlations between peak alpha frequency and the slow oscillation power phenotypes were observed (significant for peak alpha with theta power, $r_G = -.73$, $p < 7.5\text{E-}5$), and a nonsignificant positive correlation with beta power.

LD score regression based genetic correlations with a wide range of psychopathological and behavioral phenotypes with published GWAS results are shown in Supporting Information Figure S7. Significant effects were observed but failed to survive multiple testing correction (FDR or Bonferroni). Top effects included $r_G = -.35$ (uncorrected $p = .0094$, FDR $p > .10$) between theta power and autism spectrum disorder, and $r_G = .55$ (uncorrected $p = .014$, FDR $p > .10$) between beta power and generalized epilepsy. Also, a nominally significant genetic correlation between heart rate and alpha power was observed ($r_G = .22$, $p = .019$).

4 | DISCUSSION

We have presented results from the first international consortium for investigating the molecular genetic basis of brain functional activity as measured by resting EEG. The results revealed two genome-wide significant associations for Cz alpha power: on chromosome 4, a SNP intronic to *PRKG2* (rs984924), and on chromosome 7, a SNP intronic to *LINC00996* (rs10231372). FDR correction yielded 68 significant SNPs in the same *PRKG2* and *LINC00996* regions, plus intronic variants within *PCNX2* and *METTL21C*. Gene-based analyses identified multiple genes significantly associated with Cz and occipital alpha power, including *PRKG2*, *METTL21C*, and several genes in a region on chromosome 3. *PRKG2* influences anthropometric and blood pressure-related traits (Sung et al., 2015; Wood et al., 2014) and also affects multiple phenotypes in mice, including skeletal and adipose tissues. Humans with 4q21 microdeletion syndrome—which includes *PRKG2* and flanking genes—show similar skeletal symptoms, including facial bone and growth retardations, but also neuropsychological symptoms, including speech and mental retardation (Bonnet et al., 2010; Dukes-Rimsky et al., 2011).

KGG gene-based analyses implicated a high-LD region on chromosome 3 that included many significant genes associated with Cz and occipital alpha power. Variants in this region have been associated with schizophrenia and bipolar disorder. Significant brain-tissue eQTLs pointed to *ITIH4*, *GNL3*, and *GLYCTK* as genes with altered expression. MetaXcan significantly associated widespread brain expression for *ITIH4*, with hypothalamic expression reaching significance. For *GNL3*, hypothalamic and cerebellar tissues significantly associated with alpha oscillations. Hippocampal *GLYCTK* expression associated with Cz and occipital alpha. MetaXcan further associated cortical *TEX264* expression to alpha oscillations. By using expression analyses, we were able to strongly reduce the number of target genes in the chromosome 3 region from twenty-four to four, and localize their effects to hypothalamic and hippocampal expression as most strongly associated with alpha oscillations.

The association schizophrenia liability genes with oscillatory brain activity and the specific tissues with significantly altered expression highlights where oscillatory brain activity changes with increased disease risk. Altered expression of *ITIH4* in the frontal cortex in the context of schizophrenia has recently been reported (Ohi et al., 2016), and is consistent with reduced alpha oscillatory activity in the frontal cortex observed in schizophrenia (Iacono, 1982; Itil, Saletu, Davis, & Allen, 1974; Klimesch, Sauseng, & Hanslmayr, 2007; Sponheim et al., 1994; Sponheim, Clementz, Iacono, & Beiser, 2000). FDR significant SNPs were eQTLs for *ITIH4*, *GNL3*, and *MTERF4* in the frontal cortex for Cz alpha oscillations. Our results indicate that schizophrenia liability gene *ITIH4* affects oscillatory brain function and adds *GNL3* and *MTERF4* as possible target genes. Brain eQTLs further pointed to cytokine receptor genes *IL1RL1* and *IL18R1*, which are immune system genes linked to asthma, celiac disease, IBS, and atopic dermatitis (Barreto-Luis et al., 2016; Dubois et al., 2010; Liu et al., 2015; Paternoster et al., 2015). MetaXcan imputed expression analysis indicated that these genes are also brain expressed and associated with alpha oscillation power for widespread cortical and subcortical tissues, reaching significance for the Hippocampus and Putamen. The association of *IL18R1* expression with schizophrenia was reported recently (Xu et al., 2016). Our results indicate that these immunological liability genes also affect oscillatory brain function by altering widespread expression in the brain.

The results confirmed GABA_A signaling as being involved in fast oscillatory (beta) activity in the full meta-analysis ($p = .024$); however, it failed to reach significance after removing COGA, the discovery sample ($p = .052$). Interestingly, the Metaxcan expression analysis significantly associated hippocampal *GABRA2* expression to beta oscillations ($p = .0024$ and $p = .0050$ without COGA). This latter result fits well with observations that beta oscillations are influenced by GABA_A receptor $\alpha 2$ agonists such as benzodiazepines (van Lier et al., 2004; Manmaru & Matsuura, 1989; Montagu, 1972), and the crucial role of GABA_A interneurons for synchronized fast rhythms in the brain (Buzsáki & Chrobak, 1995). In our view, there is now evidence that hippocampal GABA functioning mediates the relation between resting-state EEG beta power and alcohol dependence (Dick et al., 2006; Edenberg et al., 2004; Rangaswamy et al., 2002). The selective hippocampal expression association suggests that the genetic variants affecting beta

oscillations also affect hippocampal GABA_A receptor's sensitivity to interneuron inhibition. Together, these results indicate that the association between *GABRA2* and beta oscillations is more difficult to detect in population-based samples compared to samples ascertained for alcohol use disorder. In addition, it demonstrates that eQTL based expression analysis increases power to detect associations.

Twin and family studies have consistently indicated that EEG alpha power is one of the most heritable traits in humans at up to 96% for frontal alpha power in young adult samples (Anokhin et al., 2001; van Beijsterveldt, & van Baal, 2002; Smit et al., 2005; Zietsch et al., 2007). The SNP heritability observed here using LD score regression was only able to retrieve a relatively small proportion of variance of the often highly heritable EEG traits. This pattern of high twin/family heritability with a relatively low SNP heritability has recently been observed across a range of complex, neuropsychiatric traits (Bulik-Sullivan et al., 2015a). This discrepancy could be caused by a relative large contribution of rare SNPs that are poorly tagged by the common SNP arrays used here. The SNP-based genetic correlation analysis was more consistent with twin/family studies. Strong genetic correlations ($>.70$) were observed among the slower (delta theta) and among faster oscillations (alpha beta). Results from twin studies generally ranged from 0.50 to 0.90, although the twin-based r_G between theta and delta oscillation power is generally not as strong as the SNP r_G observed here. This inconsistency between twin/family and SNP coheritability could perhaps be explained by the restricted scalp locations tested in the current analysis and/or the sample heterogeneity (e.g., COGA families ascertained through alcohol use disorders), but also the fact that only common variants were used.

Coheritability analysis showed nominally significant genetic correlations, which were no longer significant after FDR correction. This may be expected due to the relatively low sample size of this GWAS. A nominally significant genetic correlation ($r_G = .55$) was observed between beta oscillations and generalized epilepsy. This is consistent with the putative role of fast beta/gamma oscillations in ictogenesis (in the present sample only nonaffected individuals were used). The largest epilepsy GWAS to date found suggestive evidence for the involvement of *GABRA2* (ILAE Consortium, 2014), which we found to be related to beta oscillation power. GABA is a main antiepileptic drug target, and is known to affect (motor) beta EEG via GABAergic modulation of pyramidal cells (Gaetz et al., 2011; Hall et al., 2010; Rowland et al., 2013; Yamawaki, Stanford, Hall, & Woodhall, 2008). We additionally observed a significant genetic correlation between autism and theta oscillations ($r_G = -.35$, $p = .009$). Although deviant brain function in autism is most consistently found in the lower gamma band due to altered GABA inhibitory neuronal action (Blatt & Fatemi, 2011; Gandal et al., 2010; Nelson & Valakh, 2015; Rojas & Wilson, 2014), cortical and hippocampal theta/lower alpha are known to show phase-amplitude coupling with fast oscillations (gamma; Canolty et al., 2006; Khan et al., 2013; Lisman & Jensen, 2013). The significant genetic correlation ($r_G = .22$, $p = .019$) between heart rate and alpha power is consistent with observations in concurrent EEG and ECG recordings (de Munck et al., 2008).

Inherent in meta-analyses is variation in study design and ascertainment methods used across studies. Although we have homogenized the analyses as much as possible, study cohorts have used different age groups, EEG apparatus and settings during recording, different genotyping platforms and biological sampling (saliva, blood), QC protocols, as well as different imputation algorithms. Spurious relations will largely be cancelled out by the meta-analysis, and the consistent use of PCs, sex, age (group) and disease status covariates will have reduced these effects. However, remaining effects cannot be fully excluded, and may have decreased the power to detect associations. We acknowledge this limitation of our study.

In sum, we showed how genetic analyses can aid in explaining how known liability genes influence complex measures of brain functioning. We found evidence that hippocampal expression of the GABA receptor alpha 2 subunit is involved in altering beta power—consistent with its relation to epilepsy and alcohol dependence that are both well known for the involvement of GABA_A (Edenberg et al., 2004; Jurkiewicz, Gaetz, Bostan, & Cheyne, 2006). This result provides a new perspective on how GABA genes affect both beta oscillations and alcohol use disorders, with a central role for the hippocampus. Schizophrenia liability genes on chromosome 3 affected alpha oscillation power, resulting in 24 significant genes in the positional gene-based analysis. These SNPs were brain-expression eQTLs for *ITIH4*, *GNL3*, and *GLYCTK*, thus greatly reducing the number of genes that are likely to be involved. Moreover, the significant eQTLs were tissue specific, including the frontal cortex, anterior cingulate cortex, hypothalamus, and hippocampus. These results prioritize genes and brain regions for investigating how schizophrenia liability genes are expressed and influence brain activity on a systems level. Expression analysis further implicated immune system genes *IL1RL1* and *IL18R1* with altered expression in putamen and hippocampus, which highlights the role of immune system genes on brain functioning (Arion et al., 2007; Latiano et al., 2013). These genes specifically targeted subcortical structures, which in turn may influence cortical brain activity as measured with scalp-recorded EEG.

GWAS is dependent on very large sample sizes, as the effects of individual genetic variants (SNPs) are quite small, even for brain endophenotypes (Hibar et al., 2015; Stein et al., 2012). Our analyses show that prioritizing SNPs on tissue-specific expression and machine-learning approaches are useful to reveal significant genetic associations and pathways for the expression of psychiatric liability in the brain. This bodes well for future GWAS of additional EEG parameters. For example, two recently published GWASs of bipolar EEG from families of African and European ancestry reported genome-wide signal at 3q26 and 6q22, respectively (Meyers et al., 2017a; Meyers et al., 2017b). Bipolar EEG derivations show more localized activity than other EEG derivations and remove volume conduction effects, and have been particularly successful as a biomarker of alcohol dependence. Other EEG parameters of high interest are functional connectivity as biomarkers for various neurodevelopmental and psychiatric disorders. The current results indicate that finding specific molecular genetic variants related to EEG parameters is entirely feasible.

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