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An endophenotype approach to the genetics of alcohol dependence: a genome wide association study of fast beta EEG in families of African ancestry

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CONFLICT OF INTEREST

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Abstract

Fast beta (20–28 Hz) electroencephalogram (EEG) oscillatory activity may be a useful endophenotype for studying the genetics of disorders characterized by neural hyperexcitability, including substance use disorders (SUDs). However, the genetic underpinnings of fast beta EEG have not previously been studied in a population of African-American ancestry (AA). In a sample of 2382 AA individuals from 482 families drawn from the Collaborative Study on the Genetics of Alcoholism (COGA), we performed a genome-wide association study (GWAS) on resting-state fast beta EEG power. To further characterize our genetic findings, we examined the functional and clinical/behavioral significance of GWAS variants. Ten correlated single-nucleotide polymorphisms (SNPs) (r^2>0.9) located in an intergenic region on chromosome 3q26 were associated with fast beta EEG power at $P<5 \times 10^{-8}$. The most significantly associated SNP, rs11720469 (β: − 0.124; $P<4.5 \times 10^{-9}$), is also an expression quantitative trait locus for *BCHE* (butyrylcholinesterase), expressed in thalamus tissue. Four of the genome-wide SNPs were also associated with Diagnostic and Statistical Manual of Mental Disorders Alcohol Dependence in COGA AA families, and two (rs13093097, rs7428372) were replicated in an independent AA sample (Gelernter *et al.*). Analyses in the AA adolescent/young adult (offspring from COGA families) subsample indicated association of rs11720469 with heavy episodic drinking (frequency of consuming 5+ drinks within 24 h). Converging findings presented in this study provide support for the role of genetic variants within 3q26 in neural and behavioral disinhibition. These novel genetic findings highlight the importance of including AA populations in genetics research on SUDs and the utility of the endophenotype approach in enhancing our understanding of mechanisms underlying addiction susceptibility.

INTRODUCTION

Human electroencephalography (EEG) noninvasively measures ongoing resting-state brain electrical activity. These oscillations are divided into frequency bands (delta (1–3 Hz), theta (4–7 Hz), alpha (8–12 Hz), beta (13–28 Hz) and gamma (>29 Hz)), with each band reflecting a different global brain state (for example, alpha activity reflects a relaxed state while beta EEG reflects an alert awake state[1–3]). Although local excitatory–inhibitory interactions underlying sensory and motor functions involve gamma-band oscillations, cognitive functions mediated by long-range cortical interactions often involve EEG activity in the beta range.[3] Beta EEG is also associated with several externalizing disorders,[4–10] including alcohol and other substance use disorders (SUDs) and attention deficit hyperactivity disorder (ADHD). Given these associations, and the high degree of genetic influence observed in twin studies (49–85%[11,12]), beta EEG has been proposed as a useful endophenotype[13] for identifying genetic factors underlying disorders characterized by disinhibitory traits.[14]

Previous studies report differences in the magnitude of fast (>19 Hz) beta EEG among individuals with alcohol use disorders (AUD)[4–6,15,16,17] and related problems (that is, SUD, ADHD). Further, fast beta EEG was superior to the severity of illness, major depression and conduct problems in predicting relapse in abstinent individuals with a history of AUD.[5,17,18] As elevated beta EEG is present in the offspring of alcoholics prior to the onset of risky drinking,[4,15,19,20] researchers have hypothesized that excess beta power precedes the development of AUD and is likely related to an underlying genetic predisposition for developing AUD, rather than a consequence of heavy drinking. Begleiter and Porjesz[4] have suggested that this may be an electrophysiological index of an imbalance in the excitation–inhibition homeostasis in the cortex, which underlies a predisposition to develop AUD and related disorders.[4,14,20] Further supporting this hypothesis is the association of beta EEG and other disorders characterized by behavioral disinhibition: externalizing behavior in children[19] and adolescents,[7] ADHD,[10,21,22] internet addiction,[8,9] and binge drinking in emerging adults.[23]

Despite the high heritability estimates provided by twin and family studies (49–85%[11,12]), there have been relatively few genetic studies of beta EEG, and to date, only one finding has replicated. An early analysis found linkage between beta EEG and a region of chromosome 4[24] harboring variants in the gene that encodes GABA α2 (*GABRA2*).[25] More recently, a study of 586 individuals of European ancestry with Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) Alcohol Dependence (AD) and 603 controls[26] replicated the association between beta activity and *GABRA2* single-nucleotide polymorphisms (SNPs). To date, only two genome-wide association studies (GWASs) of beta EEG have been conducted.[12,27] In a study of 322 Native-American individuals, there were no genome-wide significant associations reported for beta EEG.[27] A recent GWAS of monopolar beta EEG in 4026 European ancestry adolescent twins and their parents[12] did not report any genome-wide significant variants but replicated the previous associations observed with *GABRA2*.

Importantly, there have been no GWASs of EEG conducted in populations of AA, and thus the genetic architecture of EEG-related traits is not well described in AA populations. In addition to the public health importance of including all populations in research, conducting genetic studies in populations of AA is important because of the greater genetic diversity and the evolutionary differences in disease allele frequency and linkage disequilibrium (LD) patterns observed.[28] Moreover, African-American drinkers consume less alcohol than Non-Hispanic whites but experience more alcohol-related problems, including social consequences, illness and death,[29–32] indicating a need to identify factors that mitigate risk for problem drinking. Because research examining how basic brain functioning is related to human behavior and disorders has the ultimate goal of providing prevention and/or interventions for all individuals, this important gap in the literature needs to be addressed.

Given that beta EEG is highly heritable and is related to several externalizing behaviors and SUDs, genetic analysis of beta EEG may aid in our understanding of underlying brain function in individuals at risk for a range of externalizing disorders. The primary aim of this study was to conduct a GWAS of fast beta EEG power (bipolar occipital derivation, chosen due to high heritability observed in previous studies[33]) in families of AA from the Collaborative Study on the Genetics of Alcoholism (COGA), a recently ascertained family

sample densely affected with AD and co-occurring externalizing disorders (for example, SUD, ADHD). The secondary aims of this study were to examine the functional and behavioral significance of GWAS findings.

MATERIALS AND METHODS

Collaborative Study on the Genetics of Alcoholism

COGA recruited AD probands from treatment facilities through seven participating sites, as described previously.[34,35] Institutional review boards at all sites approved the study. Participants were administered the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA), a poly-diagnostic interview.[36] Individuals aged <18 years were administered an adolescent SSAGA. In addition, DNA and EEG were collected. Principal components (PCs) derived from GWAS data were used to assign ancestry in the full genotyped sample and were the basis for the selection of AA families. A total of 99.5% of the AA (defined by PCs) individuals self-identify as 'Black/African-American' when given the following response options: 'Native American/American Indian', 'Asian', 'Pacific Islander', 'African-American/Black', 'Caucasian/White', and 'Other'. Independent of their self-reported race/ethnicity, 11.1% of the sample endorsed being of 'Hispanic or Latino descent'. The analytical sample consisted of all participants with EEG and GWAS data available, 2382 individuals from 482 families. The demographic characteristics of the full AA sample and the EEG subsample are comparable (Table 1). While 27.6% of the full AA sample met criteria for AD, rates of other co-occurring substance use and externalizing disorders (for example, cocaine dependence (CoD), ADHD) were also substantial.

EEG recording and processing

EEG recording and processing has been detailed previously.[33] Briefly, resting (eyes closed) EEG was recorded for 4.25 min; a continuous interval of 256 s was analyzed. This study focused on log-transformed absolute fast beta power (20–28 Hz) at occipital bipolar leads (O1–O2; Supplementary Figure S1). EEG procedures were identical at all collection sites.

Genotyping, imputation and quality control

Genotyping, imputation and quality control has been previously reported.[37] Genotyping of 3414 individuals from 598 families was performed at the Center for Inherited Disease Research using the Illumina 2.5M array (Illlumina, San Diego, CA, USA). SNPs with a genotyping rate <98% or that violated Hardy–Weinberg equilibrium ($P<10^{-6}$) or with minor allele frequency (MAF) <3% were excluded from the analyses. Mendelian inconsistencies were removed,[38] after which data were imputed to 1000 genomes (hg19) using SHAPEIT[39] and IMPUTE2.[40] Following imputation, genotype probabilities ⩾ 0.90 were changed to genotypes. Mendelian errors in the imputed SNPs were reviewed and resolved as described in Wetherill *et al.*[37] All SNPs with an imputation information score <0.30 or MAF <0.03 were excluded from subsequent association analysis.[40]

GWAS

GWAS was conducted in GWAF (genome-wide association analyses with family) on 12 972 748 SNPs using a linear mixed model incorporating a genetic relationship matrix to control

for the relatedness in the family sample.[41] Sex and log-transformed age (at the time of EEG recording) were included as covariates in the model, as each of these variables were associated with beta EEG ($P<0.001$). The first 10 PCs (PC1–PC10) computed from SNPRelate[42] were also included as covariates to reduce the risk of false-positives owing to population stratification. An additive genetic model was assumed. Established thresholds for genome-wide significance ($P<5 \times 10^{-8}$) were utilized. Genome-wide complex trait analysis (GCTA) was utilized to determine SNP heritability of fast beta EEG in the analytical sample. The genetic relatedness matrix was incorporated to adjust heritability estimates for familial clustering.

Functional analyses

We examined whether the most significantly associated variant for fast beta EEG was an expression quantitative trait locus (eQTL) in the UK Brain Expression Consortium (BRAINEAC; http://www.braineac.org/). Braineac draws on data from 134 neuropathologically normal individuals of European ancestry and assesses 10 different regions of the brain (Table 3).[43] Only the single SNP most associated with fast beta EEG was examined in Braineac to minimize multiple testing. Further, a Bonferonni correction was applied to all *P*-values. Associations that withstood multiple testing were examined in the Genotype-Tissue Expression Project (GTEx) database (www.gtexportal.org) to confirm eQTL findings.

Alcohol use behavior

We determined whether variants that were genome-wide associated with fast beta EEG were also associated with DSM-IV AD[44] in the discovery sample (2242 individuals from 480 families (Table 1)). Non-drinkers, those aged <18 years and unaffected individuals with 2+ SUD criteria were excluded. Analyses were performed using SAS Version 9.4 (SAS Institute (http://search.ebscohost.com/login.aspx?direct=true&db=plh&AN=101476231&site=eds-live)). Logistic regression models were adjusted for age, sex, relatedness and PC1–PC10. Given that a single phenotype was tested, we examined association with all fast beta EEG genome-wide significant SNPs. Individual *P*-values were adjusted using the P_{norm} procedure,[45] which accounts for both the LD structure of the SNPs, and the sampling of relatives. P_{norm} uses the multivariate normal distribution approximation to evaluate the significance of each test adjusting for simultaneous testing.

Next we examined whether GWAS variants were associated with DSM-IV AD in an independent sample of unrelated individuals recruited for studies of the genetics of opioid, cocaine or AD[46] made publicly accessible on dbGaP (Accession no.: phs000425.v1.p1.c1). Only individuals of AA who had AD data available were included in the analyses (1346 AD cases and 461 unaffected controls).

Finally, because of prior evidence indicating a relationship between binge drinking in young adulthood and high fast beta EEG,[23] we determined whether the top SNP meeting genome-wide criteria for fast beta EEG was associated with a measure similar to binge drinking, heavy-episodic drinking (frequency of consuming 5+ drinks within 24 h in the past year), in adolescent and young adult offspring from COGA families in COGA's prospective study.

This sample (ages 12–24 years at baseline) is longitudinally followed and has been described in detail previously.[47] The present study utilizes data from the baseline assessment of each AA individual (Table 1). Participants were asked to "Think about the last 12 months. How often did you have 5 or more drinks in a 24-hour-period?" Thirteen response options, detailed in Supplementary Table S3, ranged from 'Never' to 'Every Day'. Of the 892 individuals from 212 families, 33.8% had ever consumed a full drink of alcohol. The remaining 66.2% were coded as zero. Due to the relatively small sample size, only the single SNP most strongly associated with fast beta EEG was examined to minimize multiple testing. Association was tested with log-transformed heavy-episodic drinking, adjusted for relatedness, sex, age and PC1–PC10 in Mplus 7.4.[48]

Post hoc analyses

BCHE (and/or surrounding region, 3q26) has previously been associated with behavioral conditions relevant to fast beta EEG and AUD, including ADHD[49–52] and cocaine use/problems.[53] To determine whether the significant signal observed for fast beta EEG was accounted for by any of these disorders, we carried out three separate *post hoc* GWAS of fast beta EEG, each adjusted for one of the three disorders: DSM-IV AD, DSM-IV ADHD, and DSM-IV CoD by including it as a covariate in the model. All analyses conducted in the current study are summarized in Supplementary Table S1.

RESULTS

GWAS of beta EEG

Ten individual SNPs (pair-wise r^2>0.9 for all 10 SNPs based on hg19 1000 Genomes from the sample of African ancestry), located in an intergenic region on 3q26 (Chr 3, 166 471 942–166 489 551) were associated with fast beta EEG at $P<5 \times 10^{-8}$ (Table 2, Supplementary Table S2, Figures 1 and 2, Supplementary Figure S4). The most significant SNP was rs11720469 ($P<4.5 \times 10^{-9}$); the minor allele (G) was negatively associated with fast beta EEG (β: − 0.124; Supplementary Figure S5). Figure 2 graphically illustrates this GWAS signal, as well as the known genes located upstream and downstream of this signal, including *BCHE*, *PDCD10*, *WDR49*, *SERPINI1*, *SERPINI2* and *ZBBX*. *GABRA2* was also associated with fast beta EEG but not at a genome-wide level ($P<0.01$). GCTA estimated that 33.8% (s.e.: 0.014, $P<5.5 \times 10^{-17}$) of the variance in fast beta EEG was due to genome-wide SNPs (narrow sense heritability).

Functional analyses

In the Braineac database, rs11720469 is associated with the mRNA expression of *BCHE*, *PDCD10*, *SERPINI1*, *WDR49* and *ZBBX*. Only one of these findings survived a Bonferroni multiple test correction: rs11720469 is an eQTL for *BCHE* expression in thalamus tissue ($P = 4.20 \times 10^{-4}$); the minor allele is associated with decreased mRNA expression (Table 3). In the GTEx database, rs11720469 is associated with the expression of *BCHE* in brain tissue: cortex ($P<0.007$) and caudate ($P<0.005$). HaploReg V4.1[54,55] indicated that rs11720469 alters regulatory motifs in some cell types in the ROADMAP Epigenomics data.[56]

Alcohol use behavior

Seven of the 10 variants associated with fast beta EEG were also associated with AD in a subset of the discovery GWAS sample (Table 4); the minor allele was associated with reduced AD risk, indicating a protective effect. Given the high LD observed among these 10 SNPs, these *P*-values were adjusted for the number of tests (1.2) as estimated using the P_{norm} procedure.[45] Four of these variants survived multiple test correction: rs7428372 (β: − 0.164, *P*-value<0.037), rs11705903 (β: − 0.161, *P*-value<0.039), rs6806557 (β: − 0.161, *P*-value<0.041), and rs13093097 (β: − 0.172, *P*-value<0.027).

In an independent sample,[46] 4 of the 10 SNPs were associated with AD (Table 4). Two SNPs withstood the multiple test correction, rs7428372 (β: − 0.167, *P*-value<0.042) and rs13093097 (β: − 0.179, *P*-value<0.029); the minor allele was associated with reduced AD risk, indicating a protective effect.

Finally, having one or more copies of the minor allele was associated with reduction in heavy-episodic drinking (β: − 0.064, *P*<0.035) in the AA subsample of adolescents/young adult offspring from COGA families; however, the effect size was modest.

Post hoc analyses

In the primary GWAS sample, individuals with elevated fast beta EEG were more likely to meet criteria for DSM-IV AD, CoD and ADHD (all *P*-values <0.001, surviving Bonferroni's correction). To determine whether the significant signal observed for fast beta EEG was accounted for by one of these disorders, we carried out three separate *post hoc* GWAS of fast beta EEG, each with one of these phenotypes included as a covariate in the model. Including AD as a covariate, the 3q26 association remains but is slightly diminished (rs11720469: β: − 0.120, *P*-value: 2.2×10^{-8}; Supplementary Figure 3A). Including DSM-IV CoD as a covariate, the 3q26 association remains but is also slightly diminished (rs11720469: β: − 0.122, *P*-value: 1.3×10^{-8}; Supplementary Figure 3B). Including DSM-IV ADHD as a covariate reduced the 3q26 association (rs11720469: β: − 0.088, *P*-value: 6×10^{-4}; Supplementary Figure 3C).

DISCUSSION

Although previous studies have reported variation in beta EEG among individuals diagnosed with AD and related conditions, there have been relatively few studies examining genetic variants in relation to beta EEG and only one finding that has been replicated to date (*GABRA2*[12,26,57]). Subsequently, associations between *GABRA2*, AD[25,58–62] drug dependence[58,63] and externalizing behavior[64–67] have been observed, indicating the utility of beta EEG as an endophenotype for facilitating discovery of genes underlying disinhibitory behavior.

In what we believe is the first GWAS of fast beta EEG in families of AA, we report a genome-wide significant signal in an intergenic region on 3q26. The most significant SNP, rs11720469, was negatively associated with fast beta EEG (β: − 0.124). Interestingly, this same intergenic region has been previously implicated in a sub-threshold (that is, approaching genome-wide significant) association and gene-based association (*C3orf57*) in

the report by Hodgkinson *et al.* of monopolar beta (13–30 Hz) EEG in 322 Native Americans.[27] Note that, although the present study focused on fast beta (20–28 Hz), *post hoc* analyses indicated that the 3q26 signal is also observed at a genome-wide level for mid-beta (16–20 Hz) and at a sub-threshold level for low beta (12–16 Hz). We present Manhattan plots for the three beta frequency sub-bands in Supplementary Figure S2: (a) 12–16 Hz, (b) 16–20 Hz, and (c) 20–28, for comparison.

BCHE, thalamus and disinhibitory disorders

rs11720469 is an eQTL for *BCHE* expression in thalamus and related regions (that is, cortex, caudate). The thalamus plays a central role in relaying sensory and motor signals to the cerebral cortex,[68] reflected in EEG dynamics. Dynamic coordination of lower frequencies (theta/alpha rhythms from subcortical regions) and higher frequencies (beta/gamma rhythms from cortical sites) through a mechanism of phase–amplitude coupling modulate thalamo-cortical and corticocortical communication in the brain.[69,70] Steriade[71] reports that neuronal oscillations result from synaptic interactions in corticothalamic neuronal loops and that intracellularly recorded thalamo-cortical neurons displayed fast oscillations involving beta rhythms. Thalamic volume and/or function contributes to higher-order cognitive functions, including inhibitory control, decision-making and disinhibitory disorders.[72] Mackey *et al.*[73] reported that greater temporal discounting was associated with greater volume in a subcortical region encompassing the ventral striatum, hypothalamus and anterior thalamus. Magnetic resonance imaging studies have found that structural variation in the thalamus is related to alcohol consumption[74] and AUD,[75] as well as relapse in treatment seeking individuals with AUD.[76,77] Together, this literature suggests that the thalamus plays a key role in regulatory mechanisms underlying fast beta EEG and AUD.

In addition to AUD, *BCHE* (and/or surrounding region, 3q26) has previously been associated with behavioral conditions relevant to fast beta EEG, including ADHD and cocaine use/problems. In four independent studies, variations within or surrounding *BCHE* have also been associated with ADHD.[49–52] Jacob *et al.*[50] report that, when meta-analyzing the results of their study with three additional GWAS for copy number variations, they found that individuals with ADHD were more likely to have a deletion in the *BCHE* promoter region. Given several lines of evidence suggesting the involvement of *BCHE* in the etiology of ADHD,[50] *post hoc* we re-examined the association between 3q26 variants and fast beta EEG, adjusting for ADHD. When the GWAS of fast beta EEG included ADHD as a covariate in the model, results (Supplementary Figure S3C) show that the 3q26 association is significantly reduced, with the top SNP no longer meeting genome-wide significance criteria. This suggests an important connection between ADHD, 3q26 and fast beta EEG that future studies with longitudinal designs should disentangle (for example, does fast beta EEG mediate the association between 3q26 and ADHD?).

In addition, BChE has a key role in the metabolism of various anesthetics, muscle relaxants and cocaine.[78] Once absorbed, cocaine is rapidly transformed into two metabolites catalyzed by BChE, the enzyme produced by *BCHE.*[79] BChE is synthesized primarily in the liver and is distributed throughout the intestinal mucosa, plasma and the brain.[80] For these reasons, BChE has been conceptualized as a therapeutic agent for CoD.[53] Researchers hypothesize

that polymorphisms in *BCHE* lead to various enzyme profiles that allow different concentrations of cocaine to reach the reward system in the brain, thereby influencing susceptibility to developing addiction.[81,82] As fast beta EEG has been associated with CoD in rodents[83] and humans,[84,85] the apparent links among *BCHE*, fast beta EEG and CoD should be explored further. *Post hoc*, we examined the association between 3q26 variants and fast beta EEG, adjusted for CoD. Results (Supplementary Figure S3B) show that the 3q26 association remains, although slightly diminished, suggesting that CoD is not driving the association among 3q26 and fast beta EEG in this sample. Also of potential relevance, variations within *BCHE* have also been implicated in association studies of learning and memory,[86] cognitive functioning,[87] schizophrenia[88] and Alzheimer's disease.[89]

3q26, fast beta EEG, substance use behaviors/disorders

In COGA AA families, individuals with elevated fast beta EEG were more likely to meet criteria for AD ($P<0.01$), and a small, but significant portion of the variance shared among fast beta EEG and AD is attributable to genome-wide variants (genetic correlation, as estimated by GCTA: 0.10, s.e.: 0.17). There is evidence of association between 4 of the 10 variants meeting genome-wide criteria for fast beta EEG and AD (rs7428372 and rs13093097 survived a multiple test correction), suggesting a potential protective role for fast beta EEG variants in AD in the primary GWAS sample. Further, 4 of the 10 SNPs meeting genome-wide criteria for fast beta EEG in COGA were nominally associated with AD in an independent sample,[46] and 2 of these SNPs withstood multiple test correction. Interestingly, these two variants, rs7428372 and rs13093097 ($r^2>0.97$), were two of the four variants that withstood a multiple test correction in the discovery sample.

Association analyses of the top genome-wide significant SNP associated with fast beta EEG in the prospective sample indicated that rs11720469 was associated with heavy-episodic drinking. As this sample has an average age of approximately 17 years, this suggests that individuals with a genetic predisposition toward neuronal hyperexcitability show differences in risky drinking in adolescence/young adulthood. Previous studies indicate that compared with non-binge drinkers or mild-binge drinkers, more severe-binge drinkers have increased fast beta EEG (20–35 Hz).[23] As this fast beta power spectral pattern is also observed among those with AD,[90] the authors suggested that fast beta EEG may be a biomarker for the development of future AUDs.

These findings provide additional support for the links between fast beta EEG and alcohol use problems. Taken further, this may suggest that 3q26 harbors variants that are related to both fast beta EEG and alcohol problems (or underlying externalizing behavior, for example, ADHD). In addition, this could suggest that fast beta EEG may mediate the associations between 3q26 and alcohol problems. To assess this, *post hoc* we examined the association between 3q26 variants and fast beta EEG, adjusted for AD. Results (Supplementary Figure S3A) show that the 3q26 association remains but is slightly diminished, suggesting that AD may have an indirect role in the association of 3q26 and fast beta EEG in this sample. Stated another way, fast beta EEG may be a risk factor for some, but not all individuals with AD. These findings, along with the ADHD findings, could also indicate that the association between 3q26 and fast beta EEG is more reflective of generalized neural disinhibition, best

captured in this sample by ADHD as compared with CoD and AD. Future studies are needed to examine these hypotheses.

In light of the previous *BCHE* findings from the literature, and the evidence that rs11720469 is an eQTL for *BCHE*, this discussion has primarily focused on *BCHE*. However, there are several other potential candidate genes upstream and downstream of the GWAS signal that might harbor risk/protective variants influencing fast beta EEG and related disorders. These genes include, but are not limited to, *PDCD10*, *WDR49*, *SERPINI1*, *SERPINI2* and *ZBBX*. Given that there are two recombination hotspots between rs11720469 and *BCHE*, it is possible that *BCHE* is not directly involved in the association of 3q26 and fast beta EEG observed in this study. *WDR49* has previously been associated with quantity of visceral fat[91] and *SERPINI1* has previously been associated with variation in heart rate.[92]

Limitations

Most notable is the relatively small sample size and related lack of statistical power to detect subtle genotypic effects. However, GWAS results seem reliable based on corroborating information (that is, several genome-wide significant SNPs in high LD, biological plausibility, replication in an independent sample). Furthermore, given the nominal associations observed in eQTL analyses, these findings must be replicated in larger samples of individuals of AA. Finally, future studies should examine the effects of genetic variants on trajectories of beta EEG during development in order to delineate age-specific effects and the links between these effects and/or the onset of psychopathology (AUD, ADHD, CoD).

CONCLUSIONS

To date, there have been relatively few genetic studies examining beta EEG and only one finding that has been replicated. In addition, no previous gene identification study of beta EEG had been conducted in a population of AA. As the ultimate goal of this research is providing prevention and/or interventions for all individuals, it is crucial that AA populations are included in this work, especially because African-Americans are at greater risk for drinking-related consequences. This study found association between an intergenic signal on 3q26 and fast beta EEG in a sample of related individuals of AA. The most significant SNP is an eQTL for *BCHE*, a gene previously implicated in disinhibitory disorders and expressed in the thalamus, a brain region central to beta EEG and AUD. Further, fast beta EEG genome-wide associated variants (rs7428372 and rs13093097) were associated with AD both in the discovery sample and an independent sample. Converging data provide support for the role of genetic variants within 3q26 in neural hyperexcitability and disorders characterized by impulsivity. In addition, this study demonstrates the utility of the endophenotype approach[13]; genetic findings of fast beta EEG have provided an underlying biological hypothesis (that is, neural hyperexcitability) that can enhance our understanding of functional cerebral circuits and mechanisms underlying a predisposition to AUD and related behaviors.

Data availability

COGA data used in the current study are available from the website https://zork5.wustl.edu/coganew/contacts.html upon written request. Details regarding access to COGA data are available through the National Institute of Alcoholism and Abuse at http://www.niaaa.nih.gov.proxy.library.vcu.edu/research/major-initiatives/collaborative-studies-genetics-alcoholism-coga-study#Access. Following an embargo period, COGA data are also available from the publicly accessible dbGAP database at http://www-ncbi-nlm-nih-gov.proxy.library. vcu.edu/gap/?term = COGA (IDs: phs000763.v1.p1).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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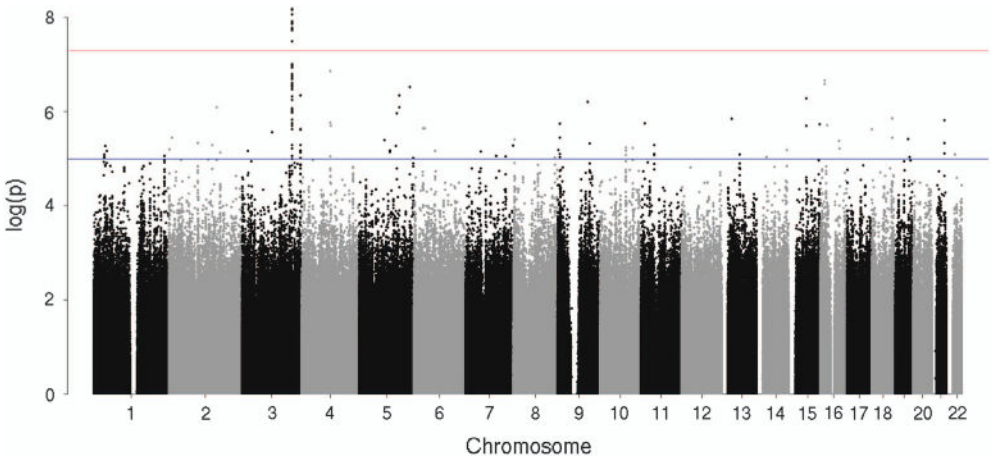

Figure 1.

Genome-wide association results for fast beta electroencephalogram in the African-American ancestry function genome-wide association study. *y* Axis denotes the –log10(*P*-value) for association. *x* Axis is the physical position of the single-nucleotide polymorphisms across the genome. Note: Red line indicates the threshold of genome-wide significance ($P<5 \times 10^{-8}$), whereas the blue line indicates the threshold of $P<5 \times 10^{-5}$.

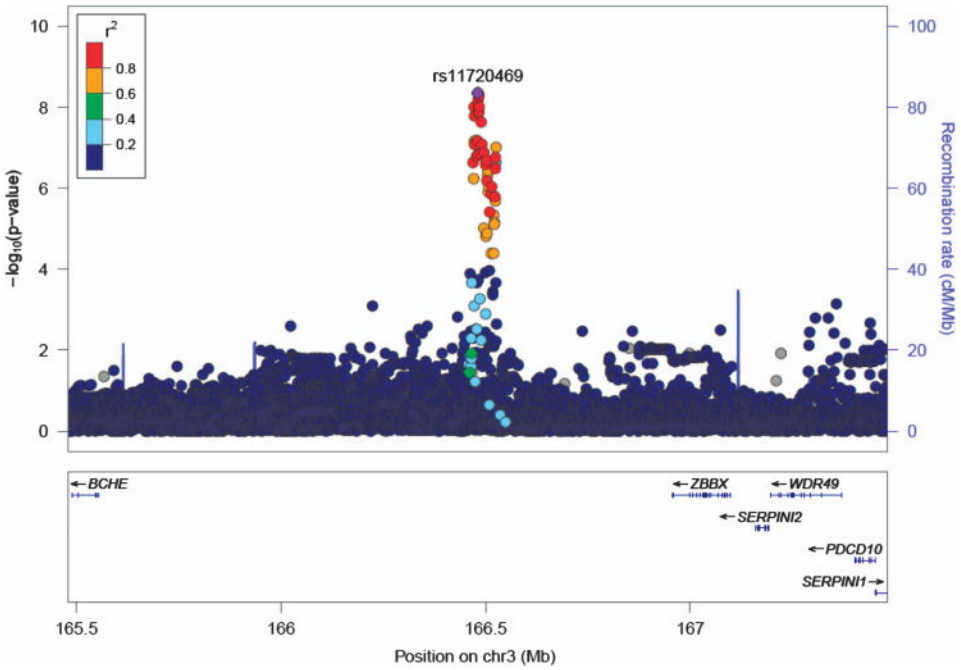

Figure 2.

Association results for fast beta electroencephalogram on chromosome 3q26. *y* Axis denotes the –log10(*P*-value) for association. *x* Axis is the physical position on the chromosome (Mb). The most significantly associated single-nucleotide polymorphism (SNP; rs11720469) is shown in purple. The extent of linkage disequilibrium (LD; as measured by r^2) between each SNP and the most significantly associated SNP is indicated by the color scale at the top left. Larger values of r^2 indicate greater LD. Circles represent *P*-values from the African-American ancestry function genome-wide association study sample. LD is based on hg19 1000 Genomes from the African sample.

Table 1

Descriptive characteristics of analytical COGA samples

	AA fGWAS genotyped sample	*AA fGWAS fast beta EEG subsample*	*AA fGWAS fast beta EEG subsample with DSM-IV data*	*AA prospective study subsample (at baseline)*
Genotyped (*N*)	3414	2382	2242	892
Families (*N*)	598	482	480	212
Female (%)	52.7%	50.3%	53.4%	52.3%
Self-identified as 'Black/African-American' (%)	99.5%	97.9%	97.4%	92.7%
Age (mean, s.d.), years	32.4 (11.2)	29.4 (12.3)	29.9 (11.8)	16.1 (3.3)
Ever drinkers	92.2%	92.3%	89.5%	33.8%
DSM-IV AD diagnosis (%)	27.6%	23.6%	24.5%	1.8%

Abbreviations: AA, African-American ancestry; AD, alcohol dependence; COGA, Collaborative Study on the Genetics of Alcoholism; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders; EEG, electroencephalography; fGWAS, function genome-wide association study.

Table 2

Summary of association results with $P<5 \times 10^{-8}$ for fast beta EEG in COGA AA families

SNP	*Bp*	*Major allele*	*Minor allele*	*MAF*	*Effect size (β)*	P-*value*
rs9859643	166 471 942	G	A	0.449	−0.121	9.90E-09
rs4680631	166 473 095	G	A	0.438	−0.119	1.60E-08
rs11720469	166 481 208	G	A	0.451	−0.124	4.50E-09
rs11705903	166 482 205	G	A	0.453	−0.122	6.40E-09
rs6806557	166 482 963	C	T	0.44	−0.12	1.40E-08
rs4680634	166 483 225	T	G	0.44	−0.121	9.90E-09
rs7428372	166 484 059	A	C	0.435	−0.124	5.30E-09
rs7430178	166 484 123	G	C	0.44	−0.12	1.30E-08
rs7430210	166 484 297	G	A	0.439	−0.121	1.00E-08
rs13093097	166 489 551	T	C	0.46	−0.117	2.30E-08

Abbreviations: AA, African-American ancestry; Bp, base pair; COGA, Collaborative Study on the Genetics of Alcoholism; EEG, electroencephalography; MAF, minor allele frequency; SNP, single-nucleotide polymorphism.

Table 3

Summary (*P*-values) of mRNA expression results for rs11720469 in the Braineac database

Gene	*CRBL*	*FCTX*	*HIPP*	*MEDU*	*OCTX*	*PUTM*	*SNIG*	*TCTX*	*THAL*	*WHMT*
BCHE	0.29	0.98	0.17	0.53	0.015	0.27	0.87	0.72	**0.001**	0.34
PDCD10	0.09	0.003	0.61	0.82	0.52	0.64	0.62	0.41	0.90	0.67
SERPINI1	0.007	0.11	0.014	0.22	0.035	0.68	0.66	0.47	0.39	0.26
WDR49	0.73	0.80	0.05	0.79	0.003	0.54	0.95	0.23	0.22	0.70
ZBBX	0.27	0.004	0.93	0.61	0.71	0.37	0.52	0.73	0.48	0.56

Note: A Bonferroni's correction was used to adjust for multiple testing; bold font denotes *P*-values that withstood this correction. In the Braineac database (http://www.braineac.org/), rs11720469 was used for expression quantitative trait locus analysis ($N = 134$ individuals of European Ancestry) of 10 different regions of the brain, including: cerebellar cortex (CRBL), frontal cortex (FCTX), hippocampus (HIPP), medulla (specifically inferior olivary nucleus; MEDU), occipital cortex (specifically primary visual cortex; OCTX), putamen (PUTM), substantia nigra (SNIG), thalamus (THAL), and intralobular white matter (WHMT). A detailed description of the samples used in the study, tissue processing and dissection is provided in Trabzuni *et al.*[43]

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Table 4

Association of fast beta EEG variants and DSM-IV AD in subset of discovery sample (N = 2242 from 480 families) and replication sample (N = 1807)

SNP	*COGA AA families*			*Gelernter* et al.[46] *sample*		
	MAF	*Effect size (β)*	P-*value*	*MAF*	*Effect size (β)*	P-*value*
rs11720469	0.451	−0.142	0.070	0.364	−0.154	0.061
rs7428372	0.435	**−0.164**	**0.037**	0.364	**−0.167**	**0.042**
rs11705903	0.453	**−0.161**	**0.039**	0.364	−0.148	0.072
rs9859643	0.449	−0.146	0.060	0.364	−0.149	0.069
rs4680634	0.440	**−0.156**	**0.046**	0.364	−0.158	0.055
rs7430210	0.439	**−0.157**	**0.046**	0.364	−0.153	0.063
rs7430178	0.440	**−0.157**	**0.046**	0.364	**−0.165**	**0.045**
rs6806557	0.440	**−0.161**	**0.041**	0.364	−0.158	0.057
rs4680631	0.438	−0.148	0.058	0.364	**−0.163**	**0.046**
rs13093097	0.460	**−0.172**	**0.027**	0.364	**−0.179**	**0.029**

Abbreviations: AA, African-American ancestry; AD, alcohol dependence; COGA, Collaborative Study on the Genetics of Alcoholism; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders; EEG, electroencephalography; GWAS, genome-wide association study; MAF, minor allele frequency; SNP, single-nucleotide polymorphism. Note: In COGA AA families, analyses were performed using SAS Version 9.4 (SAS Institute). Models were adjusted for family relatedness, age, sex and PC1–PC10. Individual P-values were adjusted using the P_{norm} procedure (Wang *et al.*[45]) that adjusts P-values for multiple testing in the context of both the linkage disequilibrium structure of the SNPs and the dependence structure owing to sampling of relatives. In the sample by Gelernter *et al.*[46] (Accession no. phs000425.v1.p1.c1), P-values were extracted from a GWAS of DSM-IV AD (Gelernter *et al.*[46]). For both samples, individual P-values that withstood the multiple test correction using the P_{norm} procedure (Wang *et al.*[45]) are represented in bold.