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ORIGINAL RESEARCH

Association Between GABRG2 and Self-Rating of the Effects of Alcohol in a French Young Adult Sample

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Purpose: Alcohol use is a leading risk factor for preventable death, injury, and disease globally. Low sensitivity to the effects of alcohol is influenced by genes and predicts risk for harmful alcohol use and alcohol use disorder (AUD). Alcohol induces effects partly by modulation of gamma-aminobutyric acid receptors type A ($GABA_A$Rs). This study investigates the relationship between genetic variation in $GABA_A$R subunit genes and individual alcohol sensitivity among French university students.

Patients and Methods: The study involved 1,409 French university students (34.5% women; mean age 20.3 years). Alcohol sensitivity was measured by the Self-Rating of the Effects of Alcohol Scale (SRE). SRE-scores from initial drinking, regular drinking, and heavy drinking were investigated for correlations with alcohol consumption and for associations with single nucleotide polymorphisms (SNPs) in $GABA_A$R subunit genes (*GABRA2, GABRG2, GABRA6*).

Results: We replicated correlations between low alcohol sensitivity and high alcohol consumption. We further found an association between the minor allele in rs211014 (*GABRG2*) and higher SRE-scores, linked to dizziness and motor incoordination. Genetic variation in *GABRG2* has previously been associated with processes involving motor coordination (alcohol withdrawal, febrile- and epileptic seizures).

Conclusion: The results from our study suggest that genetic variation in *GABRG2* may influence alcohol sensitivity, which could inform strategies for assessing risk for harmful alcohol use and AUD.

Keywords: alcohol use, GABRG2, self-rating of the effects of alcohol, genetic, AUD, AUDIT

Introduction

Alcohol use is a leading cause of preventable disability and death.[1,2] Alcohol use over time increases the risk of more than 200 diseases.[3] Alcohol use at any time increases the risk of injury and death, especially among young people.[3,4] Risk of alcohol-related harm depends on a vast interplay of factors. In particular, age, sex, socioeconomic status, comorbidities, and genetic heritability can influence how much alcohol is consumed.[4,5] Reduction of alcohol use is a global priority for the World's Health Organization.[6]

How much alcohol a person drinks is influenced by the effects of alcohol.[7] Initially, there are reinforcing disinhibitory and anxiolytic effects. Sedative effects arise with continued intake. The effects of alcohol are in turn influenced by a person's sensitivity to alcohol. Alcohol sensitivity is a phenotype that varies between people in part due to genetic factors, gender, and age.[7,8] Low sensitivity to alcohol predicts increased consumption to reach the desired effects. This results in an increased risk of alcohol-related harm and alcohol use disorder (AUD).[9–11] Alcohol sensitivity is important to investigate in young people, as they have increased sensitivity to reinforcing effects and decreased sensitivity to sedating effects of alcohol.[8,12] Alcohol

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sensitivity can be measured using the Self-Rating of the Effects of Alcohol (SRE) scale. The SRE measures the units needed to experience the effects of alcohol at baseline (drinking initiation) and during periods of moderate and heavy drinking.[12,13]

A key mechanism for alcohol-induced effects relates to alcohol's positive modulation of the inhibitory gamma-amino butyric acid receptors type A ($GABA_ARs$).[14–17] $GABA_ARs$ are found in isoforms consisting of five subunits.[18] Research suggests that the different subunits respond to different concentrations of alcohol and mediate different aspects of alcohol effects.[7,18–21] For instance, a rodent study found that mice lacking *GABRG2*-subunits displayed reduced sensitivity to GABA when exposed to alcohol, which altered dopaminergic transmission in key neuronal networks.[22] Variations in $GABA_AR$-function have been implicated in disorders such as substance use disorders, epilepsy, and anxiety.[23] Post-mortem and rodent studies have shown that $GABA_AR$-subunit expression may be related to alcohol consumption.[24,25] Of note, chronic alcohol use induces neurosynaptic adaptations, including altered expression of $GABA_ARs$.[8,26] The resulting experience of decreased alcohol sensitivity may contribute to the escalated and sustained drinking pattern seen in alcohol dependence. Increased intake would be required to achieve the desired effects, as well as to avoid the hyperexcitable state associated with drinking cessation.[16] Reduced GABAergic inhibition in key neuronal networks is considered important in the pathogenesis of AUD.[27]

Alcohol sensitivity has an estimated heritability of 50%,[13,28–30] and is used an endophenotype for alcohol-related phenotypes in genetic studies.[31,32] Few studies have explored the impact of genetic variation in GABAergic subunit genes on the effects of alcohol and even fewer on the SRE-scale specifically. However, there have been calls for replication of findings[33] and for investigation of genetic associations with SRE scales from moderate and heavy drinking periods.[7] Independent candidate gene and experimental studies have reported associations with alcohol sensitivity markers in *GABRA2*,[34–40] *GABRA4*,[41] *GABRG1*,[42] *GABRA1*,[43] and *GABRA6*.[41] GWAS results for SRE remain inconclusive so far due to relatively small sample sizes but have included nominally significant associations between initial alcohol sensitivity and a genetic marker in *GABRA6*.[44] Several studies have also identified associations between alcohol dependence and GABAergic SNPs on chromosome 4 (*GABRA2*,[33,45–50] *GABRA4*,[16] *GABRB1*,[51] *GABRG1*[42,49]) and chromosome 5 (*GABRA1*,[43,52] *GABRA6*,[53,54] *GABRG2*[33,55]). GWAS studies of alcohol-related variables have so far only reported nominal significance for GABAergic markers, but recent animal studies have identified a clear role for variation in GABAergic subunit function in risk for AUD and have highlighted a gap in knowledge as to whether risk is mediated by intermediate factors such as altered sensitivity to the effects of alcohol.[22]

In the current study, we investigated the relationship between alcohol sensitivity, drinking patterns, and genetic variations in $GABA_AR$ subunit genes.

Materials and Methods

Sample

The sample was drawn from the Susceptibility Addiction Gene Environment (SAGE) study, an observational cross-sectional cohort recruited in 2007 among college students from the French academic region Champagne-Ardenne (n=3056, 40% women, ≥18 years). The study was developed by the French National Institute of Health and Medical Research (INSERM), to detect genetic risk variants for addictive disorders. Ethical approval was obtained from the National Council for Ethic Regulation (CNIL, #907003), and the study was conducted in accordance with the Declaration of Helsinki. The participants were included based on written informed consent, and the sample was not enriched for any particular traits. Genetic information was collected using buccal swabs, and psychometric and demographic data were collected using self-report forms. The self-report forms were validated in a pilot study using a semi-structured interview, the Diagnostic Interview for Genetic Studies (DIGS),[56] administered by a trained psychologist. The cohort has previously been described elsewhere.[57,58] Participants were eligible for the current study if SRE items and gender were answered, and genetic information was obtained. Genetic variation, which is associated with ethnic ancestry, can confound results in genetic studies and lead to false-positive results, known as stratification bias. To avoid this, participants were only included if they reported not being adopted and having at least three grandparents of European origin. The study is presented according to the STREGA recommendations, a STROBE extension aimed at strengthening the reporting of genetic association studies.[59]

SNP Genotyping and Selection

Human genomic DNA was extracted from salivary samples collected using the Oragene DNA kit (DNA Genotek Inc). DNA was stored at −20°C prior to utilization, and SNPs were genotyped using the SNPlex genotyping system.[60] One percent of the sample was duplicated to measure the allele calling error rate. SNPs were excluded if the match of allele call for duplicates was less than 99%. SNPs with a call rate of less than 85% were excluded. A total of 167 of the 3056 participants had missing genotyping data.

SNP markers in the $GABA_AR$ subunit genes were selected after investigation of published associations with alcohol sensitivity and/or alcohol use in animal- and human studies. All three available SNPs were included: rs279871 (*GABRA2*), rs3219151 (*GABRA6*), and rs211014 (*GABRG2*) (Table 1). The SNPs were examined for minor allele frequency (MAF), which was compared with previously reported MAFs, and analyzed for Hardy-Weinberg equilibrium using the "hwsnp" command in Stata.[61]

Measures

Sensitivity to alcohol was measured by the SRE questionnaire[9] which is validated against alcohol challenges[9,75] and clinical interview.[76] Its psychometric properties have been shown to be reliable across generations and genders, and to predict AUD-risk in offspring of parents with AUD.[12] Participants report the number of units of alcohol required to a) begin to feel different, b) begin to feel dizzy/have difficulty articulating, and c) have difficulty walking in a coordinated manner. Effects are requested for three different time periods: 1) the first five times alcohol is consumed (SRE-5), 2) when drinking at least once a month (SRE-3), and 3) when drinking five units or more per week (SRE-H). One unit was defined as 10 grams of pure alcohol (eg, 10 cL of wine). The units reported were summed together and divided by the effects reported for each period. Two aspects of the original SRE were not included in the study survey: a fourth effect (to pass out or fall asleep) and that the period listed in 2) was defined as lasting at least three months. Possible consequences of this are discussed under limitations. For the current study, we utilized scores (continuous variable) from the SRE-5, SRE-3, and SRE-H, in accordance with suggestions for the use of SRE in genetic research.[7]

Alcohol consumption and related variables were investigated using the Alcohol Use Disorder Identification Test (AUDIT).[77] AUDIT-Consumption (AUDIT-C) is a validated screening tool and phenotype for harmful alcohol use in genetic studies[78] and consists of the first three of the ten AUDIT items (frequency of drinking, quantity consumed on a regular drinking occasion and frequency of binge drinking episodes (≥6 drinks per occasion)). The cut-off for hazardous drinking was set at 7 and 8, for women and men, respectively.[79] The remaining seven AUDIT items include three items related to biological consequences of drinking (not being able to stop drinking after starting to drink, needing a drink in the morning after drinking, having experienced blackout), three items related to biological and psychosocial consequences (failed to uphold commitments because of drinking, feeling guilt or remorse after drinking,

Table 1 Overview of Included SNPs

dbSNP ID	Position (GRCh38)	Gene	Alleles	MAF SAGE	MAF Databases[a]	HWE p-value[b]	Protein Domain	References
rs279871	4:46303716	*GABRA2*	T/C	0.439	0.425	*0.257*	Intron variant	Association with subjective effects of alcohol,[34–39] AUD,[33,45,49,50,62] drinking prediction,[63,64] and altered *GABRA2* expression.[65]
rs211014	5:162149412	*GABRG2*	C/A	0.236	0.246	*0.921*	Intron variant	Association with alcohol dependence,[33,66,67] heroin dependence[68] epileptic and febrile seizures.[69–72]
rs3219151	5:161701908	*GABRA6*	C/A	0.450	0.453	*0.964*	3 prime UTR-variant	Association with alcohol dependence,[33] drinking quantity,[73] AUD and *GABRA6*-expression[65] and epilepsy.[74]

Notes: [a]MAF ALFA from https://www.ncbi.nlm.nih.gov/snp/. [b]Pearson's χ^2- test.

Abbreviations: SNP, Single Nucleotide Polymorphism; GRCh38, Genome Reference Consortium Human Build 38; MAF, Minor Allele Frequency; SAGE, Susceptibility Addiction Gene Environment-cohort; HWE, Hardy Weinberg Equilibrium; AUD, Alcohol Use Disorder, UTR, Untranslated Region.

having hurt yourself or others because of drinking), and one psychosocial item (having received concerns about drinking from those around you). All AUDIT-variables were treated as continuous variables. Questions about the frequency of the incidents could be answered with the following responses: 1) never, 2) less than monthly, 3) monthly, 4) weekly, and 5) daily, scored from 0 to 4. Finally, we included age at first drink (continuous) which is considered to be a predictor of AUD.[8,80]

Covariates included: Gender (self-reported, categorical: woman/man) was used as a stratification variable for descriptive analyses. As gender was self-reported, we use the terms woman/man when referring to our own data, as opposed to genetically determined sex, which would have been reported as female/male. Other covariates included age (continuous), BMI (continuous), and socioeconomic background, as indicated by parental education (highest level of parental education for mother and/or father, dichotomized into higher education (≥ college): yes/no).

Statistical Considerations

Variable Inspection and Tests

Variables were first checked for missing data and outliers. SRE scores were inspected in scatterplots against AUDIT-C-scores and removed if considered as outliers (visualized as isolated or inconsistent high SRE-scores on one or more SRE items and low AUDIT-C scores (n=43)). Missing data on alcohol-related variables led to exclusion from the specific analysis, as answers to alcohol items are considered to be missing not at random.[81] This can lead to misleading results in multiple imputation-methods. Further, single imputation can inflate the mean, which reduces variance, leading to erroneous results.[82] Secondly, the variables were checked for deviations from the assumptions underlying the different statistical methods. Nonparametric tests were chosen for genetic association analysis, due to the distribution and differences in variance of the SRE-scales between allelic genotypes. *Kruskal–Wallis equality of population rank test* was used for association test with SNPs when considering the three different alleles (eg AA vs AC vs CC) and Wilcoxon rank sum test for recessive/dominant model testing (eg AA vs AC+CC). The assumptions for both methods were met by the data. For the other data that met requirements for parametric testing, Chi-squared test was used to compare categorical variables (gender, parental education, parental alcohol problem, genetic variation markers), analysis of variance (ANOVA) to compare categorical to continuous variables (age, BMI, age at first drink, AUDIT-items, SRE-5, SRE-3, and SRE-H) and linear regression to compare continuous variables. Correlation analyses were conducted using Pearson correlation coefficient.

The significance threshold for genetic association analysis was set using the Holm-Bonferroni correction (α/(n-rank +1, $\alpha = 0.05$, n = 17 tests) and evaluated using the resulting p-values. Power analyses were not performed prior to compilation of the original study and the results of the current study (mean, standard deviation, and sample size) were used to perform a post-hoc power analysis. The shortcomings of this approach are discussed under limitations.

Statistical Analysis

Statistics were performed using Stata version 17 (Stata Corp, 2017), with the exception of correlation analysis, which was performed in R Studio (version 4.3.2, https://www.r-project.org/). First, descriptive statistics of the sample were performed, stratified by gender and compared statistically. Second, alcohol-related variables were investigated for correlation, based on pairwise complete observations. Results were visualized by the *corrplot* package in R.[83] Third, genetic association analysis was performed without the assumption of an effect model (genotypes coded as 0: homozygote common allele,1: heterozygote, 2: homozygote minor allele). Gene variants that showed nominal significance with alcohol sensitivity were further examined for pattern of effect, which led to testing of binary dominant or recessive model (coded as 0: not carrying effect allele,1: carrier of effect allele, either both alleles (recessive model) or one (dominant model)).

Results

The sample (n=1409, 34.5% women) had a mean age (standard deviation, SD) of 20.3 (1.2) years (Table 2). All SNPs were in Hardy-Weinberg equilibrium with minor allele frequencies (MAF) comparable to dbSNP databases (Table 1). Compared to women, men reported a younger age of first drink (13.3 men, 13.8 women, $p < 0.001$), higher scores on

Table 2 Description of the Study Population (n=1409)

Variables	Measurement	Men (n=923)	Women (n=486)	*p-value*
Age (years)	Mean (SD)	20.25 (1.21)	20.30 (1.21)	*0.457*[a]
Parents higher education	n (%)	395 (45.4)	180 (38.3)	*0.012*[b]
BMI (kg/m^2)	Mean (SD)	22.58 (3.12)	21.43 (3.12)	*<0.0001*[a]
Age at first drink	Mean (SD)	13.26 (2.83)	13.80 (2.65)	*<0.001*[a]
SRE-5	Mean (SD)	6.29 (2.98)	4.74 (2.33)	*<0.0001*[a]
SRE-3	Mean (SD)	8.84 (3.70)	6.12 (2.85)	*<0.0001*[a]
SRE-H	Mean (SD)	11.54 (5.75)	8.23 (4.77)	*<0.0001*[a]
AUDIT 1 - Drinking frequency	Mean (SD)	2.66 (0.76)	2.13 (0.86)	*<0.0001*[a]
AUDIT 2 – Drinking quantity	Mean (SD)	1.67 (1.41)	0.89 (0.99)	*<0.0001*[a]
AUDIT 3 – Binge drinking frequency	Mean (SD)	1.66 (0.97)	0.98 (0.93)	*<0.0001*[a]
AUDIT C-score	Mean (SD)	6.03 (2.44)	4.02 (2.16)	*<0.0001*[a]
AUDIT C – cutoff (≥7 women, ≥8 men)	n (%)	281 (30.9)	67 (14.1)	*<0.0001*[b]
AUDIT4 – Not able to stop drinking	Mean (SD)	0.40 (0.78)	0.24 (0.57)	*<0.0001*[a]
AUDIT5 – Failed tasks due to drinking	Mean (SD)	0.40 (0.66)	0.31 (0.57)	*0.012*[b]
AUDIT6 – Need for drink morning after	Mean (SD)	0.15 (0.49)	0.05 (0.28)	*<0.0001*[a]
AUDIT7 – Guilt after drinking	Mean (SD)	0.43 (0.66)	0.31 (0.56)	*<0.001*[a]
AUDIT8 – Experienced blackout	Mean (SD)	0.65 (0.75)	0.46 (0.70)	*<0.0001*[a]
AUDIT9 – Injured self or others	Mean (SD)	0.51 (1.19)	0.35 (0.99)	*0.0126*[a]
AUDIT10 – Other people worried	Mean (SD)	0.24 (0.90)	0.12 (0.62)	*0.007*[a]
AUDIT P-score	Mean (SD)	2.77 (3.19)	1.83 (2.59)	*<0.0001*[a]
AUDIT-score	Mean (SD)	8.80 (4.85)	5.88 (4.06)	<0.0001[a]

Notes: [a]Analysis of variance (ANOVA) – test. [b]Pearson χ^2- test.

Abbreviations: SD, Standard Deviation; BMI, Body Mass Index; SRE, Self-Rating of the Effects of Alcohol Scale; SRE-5, First five times of consumption; SRE-3, When drinking at least once a month; SRE-H, When drinking more than five drinks per week; AUDIT, Alcohol Use Disorder Identification Test. AUDIT C, AUDIT Consumption (AUDIT items 1–3); AUDIT P. AUDIT Problems (AUDIT items 4–10); Missing: BMI (19); Parental education (69); SRE-first (157); SRE-regular (448); SRE-heavy (875); AUDIT1 (7); AUDIT2 (12), AUDIT3 (8); AUDITC (23); AUDITC cut-off (23); AUDIT4 (9); AUDIT5 (12); AUDIT6 (10); AUDIT7 (7); AUDIT8 (13); AUDIT9 (4); AUDIT10 (2); AUDIT score (53).

SRE subscales and AUDIT items. SRE subscales differed in all time periods recorded, with differences increasing from initial drinking to heavier drinking periods (SRE-5: 6.29 (4.74) men, 4.74 (2.33) women; SRE-3: 8.84 (3.70) men, 6.12 (2.85) women; SRE-H: 11.54 (5.75) men, 8.23 (4.77) women; all $p < 0.0001$). The sum of AUDIT items 1, 2, and 3 (AUDIT C) was 6.03 (2.44) for men and 4.02 (2.16) for women ($p < 0.0001$), corresponding to 30.9% of men and 14.1% of women above the cut-off for harmful alcohol use.

Correlations between SRE, AUDIT, and age at first drink are shown in Figure 1. First, SRE-subscales were strongly correlated: SRE-3 and SRE-H ($r = 0.85$), SRE-3 and SRE-5 ($r = 0.74$) and SRE-5 and SRE-H ($r = 0.57$) (all $p < 0.001$). SRE-5 displayed positive correlations with AUDIT2 (number of drinks per occasion) ($r = 0.12$, $p < 0.001$), AUDIT3 (frequency of binge drinking) ($r = 0.12$, $p < 0.001$), and AUDIT6 (need for a drink the morning after drinking) ($r = 0.07$, $p < 0.05$). SRE-3 correlated positively with AUDIT1 (frequency of drinking) ($r = 0.16$, $p < 0.001$), AUDIT2 ($r = 0.26$, $p < 0.001$), AUDIT3 (binge drinking) ($r = 0.25$, $p < 0.001$), AUDIT4 (not being able to stop after starting drinking) ($r = 0.09$, $p < 0.01$), AUDIT6 ($r = 0.11$, $p < 0.001$), AUDIT8 (experiencing blackouts) ($r = 0.1$, $p < 0.01$) and AUDIT-C cut-off for hazardous alcohol consumption ($r = 0.17$, $p < 0.001$). Finally, the SRE-H showed positive correlations with AUDIT1 ($r = 0.1$, $p < 0.001$), AUDIT2 ($r = 0.24$, $p < 0.001$), AUDIT3 ($r = 0.21$, $p < 0.001$), AUDIT4 ($r = 0.11$, $p < 0.05$), AUDIT6 ($r = 0.12$, $p < 0.01$), AUDIT8 ($r = 0.09$, $p < 0.05$) and AUDIT-C cutoff ($r = 0.15$, $p < 0.001$). Age at first drink showed negative correlations with AUDIT1 ($r = -0.19$, $p < 0.001$), AUDIT3 ($r = -0.14$, $p < 0.001$), AUDIT5 ($r = -0.08$, $p < 0.01$), AUDIT6 ($r = -0.12$, $p < 0.001$), AUDIT8 ($r = -0.09$, $p < 0.01$), AUDIT9 ($r = -0.09$, $p < 0.001$), and AUDIT10 (having other people worry about your drinking) ($r = -0.07$, $p < 0.01$). Age of first drink did not correlate with any SRE-measures, but correlated negatively with AUDIT1 ($r = -0.19$, $p < 0.001$), AUDIT3 ($r = -0.14$, $p < 0.001$), AUDIT5 ($r = -0.08$, $p < 0.01$), AUDIT6 ($r = -0.12$, $p < 0.001$), AUDIT8 ($r = -0.09$, $p < 0.01$), AUDIT9 ($r = -0.09$, $p < 0.001$), AUDIT10 ($r = -0.07$, $p < 0.01$), and AUDIT-C cut-off ($r = -0.11$, $p < 0.001$).

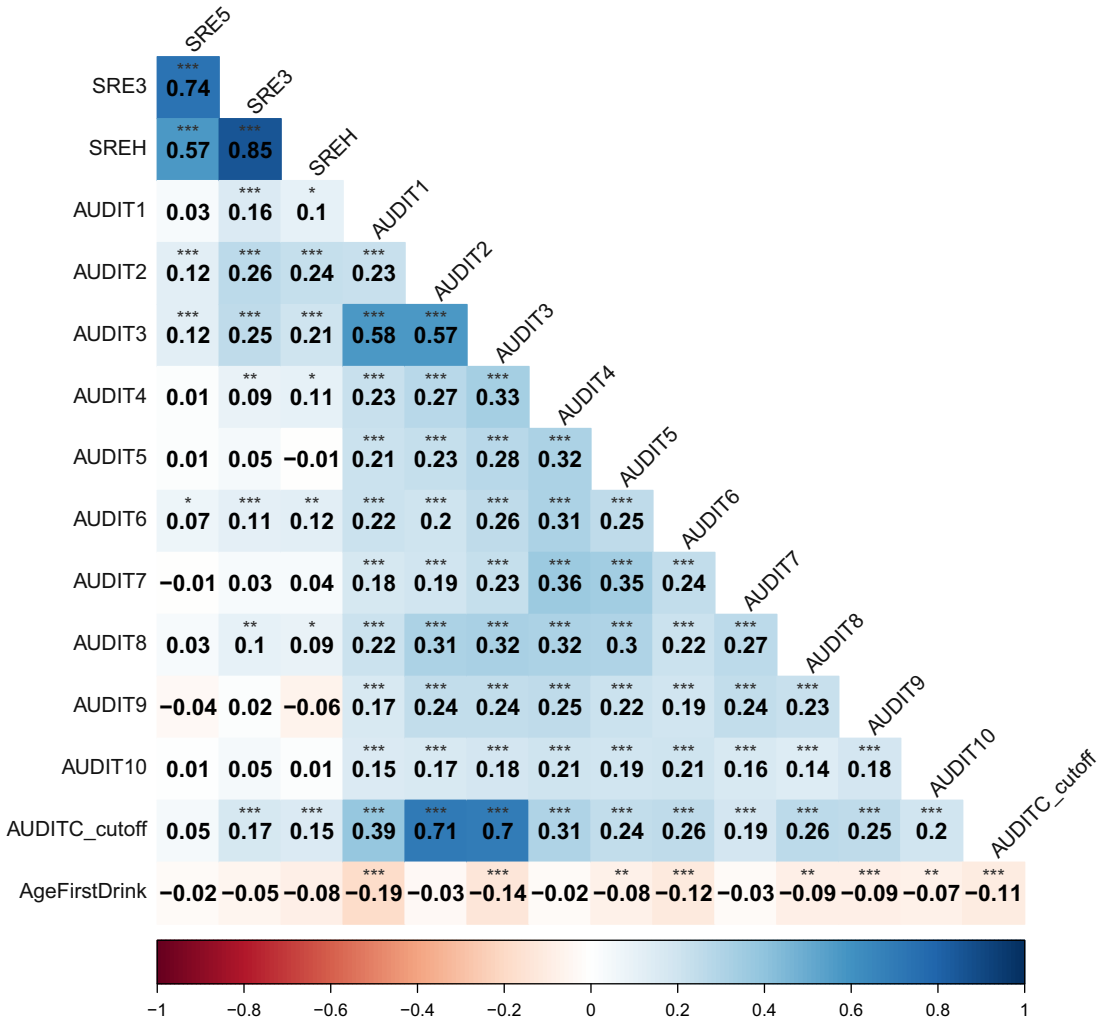

Figure 1 Pearson correlations between SRE subscales, AUDIT items and Age of first drink.
Notes: Significance level: * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$. Based on pairwise complete observations. SRE subscales mainly correlate with quantity measures and, to a lesser extent, frequency measures, in addition to showing a significant correlation with the cut-off for hazardous drinking. Further, AUDIT6 (needing a drink the morning after) and AUDIT8 (experiencing blackouts) correlate with SRE-3 and -H. Age at first drink correlates negatively with AUDIT1, 3, 5, 6, 8, 9, and 10.
Abbreviations: SRE, Self-Rating of the Effects of alcohol Scale; SRE-5, First five times of consumption; SRE-3, when drinking at least once a month; SRE-H, when drinking more than five drinks per week; SD, Standard deviation; AUDIT1-10, Alcohol Use Disorder Identification Test items 1–10.

Genetic association analysis showed a significant association between rs211014 (*GABRG2*) and SRE-heavy ($p = 0.008$) (Table 3). The effect of the minor allele followed a recessive pattern. The same SNP trended towards association with SRE-3. The recessive model (Table 4) was associated with SRE-H ($p = 0.002$) and showed a nominally significant association with SRE-3 ($p = 0.026$). Analysis of individual SRE-items showed that the genetic association signal was related to feeling dizzy/difficulty articulating (SRE-3, $p = 0.0036$ and SRE-H, $p = 0.0008$) and feeling uncoordinated (SRE-H, $p= 0.0033$). Carriers of the minor allele reported a significantly higher number of units before experiencing an effect. After correction for multiple comparisons (Holm–Bonferroni method, level of non-rejection of H0 = 0.0039, by test rank 5), the following association remained significant: between the recessive SNP-model and the SRE-H subscale, the SRE-3 item feeling dizzy/having problems articulating and the SRE-H items feeling dizzy/having problems articulating and feeling uncoordinated. Post hoc power analysis showed that for the given mean, standard deviation, and sample size of SRE-H for the recessive model of rs211014, our study had 79.6% power at the 0.05 significance level.

Table 3 Genetic Association Analysis SNP Genotype and SRE-Subscales

dbSNP ID	n	SRE subscale	Mean (SD)			*p-value*[a]
			Homozygote Major Allele	Heterozygote	Homozygote Minor Allele	
rs279871	1224	SRE-5	5.75 (2.94)	5.76 (2.84)	5.64 (2.82)	*0.846*
	937	SRE-3	8.09 (3.66)	7.93 (3.62)	8.11 (3.95)	*0.841*
	521	SRE-H	10.60 (5.91)	10.94 (5.63)	10.73 (5.86)	*0.620*
rs211014	1235	SRE-5	5.71 (2.95)	5.73 (2.68)	5.93 (3.12)	*0.663*
	945	SRE-3	7.93 (3.84)	7.88 (3.29)	9.16 (4.04)	*0.071*
	524	SRE-H	10.52 (5.79)	10.67 (5.42)	14.04 (6.23)	*0.008*
rs3219151	1239	SRE-5	5.91 (2.92)	5.65 (2.84)	5.70 (2.87)	*0.333*
	951	SRE-3	8.24 (3.71)	7.90 (3.56)	8.04 (3.99)	*0.406*
	529	SRE-H	11.01 (5.32)	10.44 (5.43)	11.28 (6.92)	*0.458*

Notes: [a]Kruskal–Wallis equality of populations rank test, reported with ties, unadjusted.
Abbreviations: SNP, Single Nucleotide Polymorphism; SRE, Self-Rating of the Effects of Alcohol Scale; SD, Standard Deviation; SRE-5, First five times of consumption; SRE-3, When drinking at least once a month; SRE-H, When drinking more than five drinks per week; SD, Standard deviation.

Table 4 Recessive Model rs211014 (GABRG2) Association with SRE-Items

Variables	Recessive Model rs211014 Mean (SD)		*p-value*[a]
	0	1	
SRE-3	7.91 (3.64)	9.16 (4.04)	*0.026*
Feeling different	5.02 (2.75)	5.52 (2.01)	*0.199*
Dizzy / trouble articulating	8.07 (3.93)	9.73 (4.36)	*0.0036**
Incoordination walking	10.74 (5.41)	12.19 (6.12)	*0.088*
SRE-H	10.57 (6.23)	14.04 (6.23)	*0.002**
Feeling different	7.25 (4.47)	8.41 (4.41)	*0.143*
Dizzy/trouble articulating	10.63 (6.00)	14.70 (7.80)	*0.0008**
Incoordination walking	13.92 (7.73)	18.85 (8.82)	*0.0033**

Notes: [a]Wilcoxon Rank-Sum test. *Significant after adjustment for multiple comparisons (Holm–Bonferroni).
Abbreviations: SRE, Self-Rating of the Effects of alcohol Scale; SD. Standard Deviation; SRE-3, When drinking at least once a month; SRE-H, When drinking more than five drinks per week.

Discussion

This study investigated alcohol sensitivity as measured by the SRE questionnaire for correlations with alcohol-related variables and associations with GABAergic genetic variants, in a sample of French students. The results showed higher scores in men compared to women on subjective alcohol sensitivity and AUDIT items, indicating lower sensitivity to alcohol, increased consumption, and more adverse experiences related to alcohol use. We found a positive correlation between the SRE and consumption quantity, frequency, and AUDIT items related to consequences of increased quantity. The study demonstrated an association between rs211014 (*GABRG2*) and the SRE, where homozygosity for the minor allele indicated a lower level of response to alcohol mainly related to motor incoordination, significant after correction for multiple comparisons.

Contextualization and Relevance of Alcohol Variables

The results of our study are similar to what previous studies on age matched samples have found for SRE scores,[12,76] AUDIT-C cut-offs,[79] and correlations between SRE scales,[84] which provide ground for comparisons with other studies. We confirmed the SRE score as a weak to moderate predictor of the amount of alcohol consumed, in addition to a weak effect on the frequency of drinking. Our results thus provide additional support for a connection between low alcohol sensitivity and increased alcohol consumption. This has been demonstrated in previous studies.[11] To report to be able to drink more units of alcohol in periods of moderate and heavy consumption correlated with being above the cut-off for hazardous drinking. This is of importance to current global actions to reduce harmful use of alcohol targeting youth, as

alcohol sensitivity per now is not included as a perspective in the WHO Global Alcohol Action Plan 2022–2030.[85] Our results further support the role of age of first drink as an important marker for alcohol-related harm.[80,86] While some studies have not found evidence for this connection,[87] our study found consistent results that older age of first drink was associated with reduced scores on important AUDIT items such as frequency, binging, and several adverse outcomes.

Alcohol Sensitivity and Gender

The descriptive findings highlight conflicting aspects of how men tolerate alcohol compared to women, and how low alcohol sensitivity might increase the risk of AUD. Men report lower alcohol sensitivity, and studies show that men can drink the same amounts as women with lower resulting BAC.[12] It is therefore not surprising that men drink more, as more might be needed to achieve the desired effects. Interestingly, another study by the authors of the current study found that low alcohol sensitivity in a male sample may be associated with increased presystemic metabolism of alcohol, leading to a lower BAC.[88] One could speculate that in controlled experiments, low alcohol sensitivity is associated with lower BAC, whereas in real-life settings with free access to alcohol, low alcohol sensitivity is associated with drinking more to get the wanted inebriation. This could overload the presystemic first-pass effect or other biological mechanisms associated with low alcohol sensitivity, increasing brain alcohol exposure and the risk of AUD.

GABRG2-Variation Associated with SRE-3 and SRE-H

Genetic variation in $GABA_A$Rs has been implicated in alcohol sensitivity and the risk of AUD.[23,89] We found an association between lower alcohol sensitivity during moderate and heavy consumption periods and homozygosity for the minor allele of rs211014. rs211014 is located in intron 8 of the *GABRG2* gene on chromosome 5. It codes for the γ2 subunit, a component of the most widely distributed constellation of the $GABA_A$Rs.[90] This subunit has been shown to be critical for neuronal maturation,[91] synaptic receptor localization, and maintenance of overall $GABA_A$R function.[92] Previous studies have shown that the *GABRG2*-subunit is sensitive to high doses of alcohol.[93]

GABRG2-variation has been associated with increased risk of AUD, possibly through endophenotypes such as altered sensitivity to the effects of alcohol.[22] Li et al found that rs211014 was associated with both alcohol- and heroin dependence,[33] suggesting a role in the pathogenesis of dependence, however not replicated in a meta-analysis. A quantitative trait locus mapping study found that genetic variation in *GABRG2* was related to alcohol withdrawal severity in mice,[94] and in another study found to predispose to acute alcohol withdrawal, ethanol-induced motor incoordination, -taste aversion, and -hypothermia.[95] In our study, the association with *GABRG2*-variation was related to the SRE-items covering dizziness/difficulty articulating and motor incoordination, indicating that genetic variation in *GABRG2* may affect alcohol-induced motor inhibition. To date, rs211014 has not been found in GWAS for alcohol consumption or AUD, and results from SRE/alcohol sensitivity studies remain inconclusive, as larger samples are required. However, this and other SNPs in *GABRG2* are robustly associated with risk of epilepsy and febrile seizures, supporting their relevance to motor inhibition. Up to half of all cases of epilepsy are caused by genetic variation,[96,97] and in particular variation in γ2.[98] rs211014 was detected at near genome-wide significance (10^{-6}), in a GWAS study of epilepsy,[97] and genetic variation in *GABRG2* was one of seven loci replicated in the largest febrile seizures GWAS to date,[69] in addition to replications in several candidate gene studies.[69–72,99] *GABRG2*-related epilepsy is predominantly fever-sensitive and responds to medication, which also regulates $GABA_A$R-signalling.[100]

The functional consequence of the genetic variation marked by rs211014 could be speculated on by looking at associations with alcohol sensitivity, alcohol withdrawal, and epilepsy, all of which are associated with reduced GABAergic motor inhibition. As noted above, *GABRG2* is essential for $GABA_A$R's dominant role in inhibitory signaling, and fast synaptic inhibition is primarily mediated by receptors containing γ2 subunits.[101] Alcohol induces many of its effects by potentiating GABA inhibitory signaling. For alcohol sensitivity, a condition associated with reduced GABAergic signaling could indicate an increased need for alcohol to achieve effects. For example, the level of phosphorylation of the γ2 subunit has been shown to influence the effects of alcohol.[26] In epilepsy, less effective GABAergic signalling could lower seizure thresholds.[102] Finally, alcohol withdrawal is a state associated with hyperexcitability due to cessation of alcohol inhibition,[103,104] and a less effective inhibitory signalling could predispose to withdrawal seizures. In addition, a recent study found an over-representation of genes involved in seizures and epilepsy in mice with low and high susceptibility to alcohol withdrawal.[105] Taken together, though

grossly simplified for the purposes of discussion, the evidence points to genetic variation in *GABRG2* and altered GABAergic inhibitory signalling affecting motor inhibition. It could be speculated on if low sensitivity to alcohol's effect on motor coordination potentiates increased consumption due to lack of negative feedback, which then could be linked to prospective AUD risk via other molecular mechanisms, such as increased reinforcing effects.

To succeed in reducing harmful use of alcohol, future studies on alcohol sensitivity and the effects on a genetic and molecular level are important in order to understand mechanisms leading to increased consumption, crucial for preventive strategies. First, studies investigating full alcohol sensitivity profiles, including negative and reinforcing effects as well as subjective and objective measurements, are of importance, linked with data from validated alcohol questionnaires mapping consumption quantity, pattern, and consequences. Experimental studies of first-pass metabolism among young adults could further highlight biological differences among people reporting high and low alcohol sensitivity. Future studies on *GABRG2*-variation and $GABA_A$ function could improve knowledge on alcohol's potential to induce different sensitivity profiles based on its effect on signalling systems across the cerebrum and cerebellum. Increased understanding of the $GABA_A$ receptor could further have life-saving clinical importance. Of note, there have been a call to action for research targeting alcohol withdrawal-related seizures.[106] It may be interesting to investigate genetic variation in the γ2-unit and alcohol withdrawal seizures, as recent studies have shown that elevated temperature, a risk factor for alcohol withdrawal seizures,[107] can alter expression of $GABA_AR$ subunits in *GABRG2* knock out mice,[108] and that *GABRG2*-variation may be associated with temperature-dependent-seizures.[99] Lastly, longitudinal studies or investigation of *GABRG2*-variation in a sufficient sample of people meeting criteria for AUD would be crucial to establish the significance of genetic variation in *GABRG2* and AUD-risk. Future genetic studies should ensure participation from different ethnicities, as the majority of large biobanks have data from participants with European ancestry. This is an obstacle for robust results, generalization of results and equity in medical research.[109–111] It is particularly important for alcohol research, as harmful use of alcohol is a global challenge for all ethnicities.

Limitations and Strengths

The current study may be limited by selection bias as it includes students from Champagne-Ardenne of European origin, which affects generalization to other ethnicities. Champagne-Ardenne is a region with a long history of alcoholic beverage production, which could influence drinking culture.[112] In particular, this could affect unit definitions and the expected effects of alcohol. The altered SRE item for SRE-3 could introduce a bias affecting comparisons with other studies due to the shorter required observation period, where a three-month requirement could affect tolerance development between sessions, as opposed to the one month used in the current study. Furthermore, the SRE questionnaire did not include the final item in the original SRE score, which deals with "to pass out", which could introduce a downward bias as the number of units required to pass out would be expected to be higher than the numbers reported for the other items. However, alcohol-related passing out could be related to different degrees of amnesia (grayouts or blackouts) which would make responses to this item unreliable, supporting its exclusion.[113] Due to the young age of our sample and consequently the low proportion meeting criteria for dependence, we were not able to examine associations between *GABRG2* and AUD. Furthermore, self-reporting of grandparents' ethnicity as a basis to avoid population stratification is not optimal but was the best alternative as asking a participant about their ethnicity is not permitted under the French law and no additional genomic information was available to control for this. There were also no controls for association/relatedness. Power analysis was not conducted prior to sample assembly, adding to the limitations of the candidate gene approach, which has historically been hampered by false positives, over estimation of effect sizes, and failure to replicate results. Lastly, all non-genetic data were from self-report forms from participants who agreed to participate, which could lead to different sources of bias such as recall bias, non-response bias, and volunteer-bias. Strengths of the current study include the quality of the psychometric instruments, genotyping, and response rate in the original sample, as well as consistent, replicated results across variables that remained significant after correction for multiple comparisons. In particular, the genetic variation detected in the current study has a GWAS-replicated association with comparable traits and provides substance for future interdisciplinary research. Furthermore, to our knowledge, this is the first study to investigate genetic associations with SRE-3 and SRE-H. The importance of reduced heterogeneity – deep phenotyping as opposed to broad phenotyping – is increasingly emphasised,[114] and in the current study we aimed to minimize heterogeneity by linking signal to specific effect and found that feeling dizzy/difficulty articulating and walking provided the

strongest association. This is consistent with suggestions that genetic research may benefit from "greater phenotypic granularity" as noted by Kember et al,[115] which often requires smaller, deeply phenotyped samples.

Implications of Research

Our results on the association between low, subjective alcohol sensitivity and increased alcohol consumption should be considered in preventive strategies for reducing harmful alcohol use. Knowledge about hereditary, biological differences related to the effects of alcohol, could empower youth when making choices about alcohol consumption. *GABRG2*-variation could be a molecular target for alcohol's effect on motor inhibition, which warrants further research to elaborate on clinical implications for alcohol sensitivity and AUD.

Conclusion

Overall, our study affirms the SRE-questionnaire as an effective tool to predict hazardous drinking, primarily through increased number of drinks per occasion. We further underline gender differences in alcohol sensitivity, consumption patterns, and alcohol-related adverse effects, and suggest that current language regarding alcohol sensitivity needs to be reframed to highlight that men are less resilient than women to the overall effects of alcohol. Our study identified genetic variation in the γ2 subunit as potentially important for reduced alcohol sensitivity to alcohol's effect on motor inhibition, pointing to the need for interdisciplinary research targeting GABAergic inhibition, alcohol sensitivity, seizure activity, and alcohol withdrawal, with the potential for clinically relevant outcomes for individuals with AUD. Future studies investigating motives for drinking, subjective and objective effects of alcohol, in limited and unlimited access to alcohol may be of interest to further understanding of the impact of low alcohol sensitivity. The use of alcohol sensitivity questionnaires such as the SRE, highlighting men's overall tolerance of alcohol, and knowledge about biological differences in responses to alcohol, could be important aspects to include in strategies aimed at empowering youth when working towards reducing harmful use of alcohol.

Ethics Approval

The study was conducted in accordance with the Declaration of Helsinki and received approval from the National council for ethic regulation (CNIL, #907003).

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Disclosure

Prof. Philip Gorwood reports personal fees from Angelini, personal fees from Janssen, personal fees from Newron, personal fees from Otsuka, personal fees from Lundbeck, outside the submitted work. The authors report no conflicts of interest in this work.

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