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RESEARCH REPORT

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# Electrophysiological sexual dimorphism as an early risk marker of alcohol use in adolescence: A longitudinal neuroimaging study

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## Abstract

**Aims:** To identify the brain activity profiles associated with alcohol consumption and to address its causes. Furthermore, we sought to examine the relationship between these electrophysiological markers and the excitation–inhibition balance, as well as to explore the potential moderating role of sex in these associations.

**Design:** Longitudinal study involving a neuroimaging assessment that included magnetoencephalography (MEG) and magnetic resonance imaging (MRI), along with a battery of self-report questionnaires. A follow-up assessment was conducted two years later using the same set of neuroimaging and behavioural measures.

**Setting and participants:** 56 adolescents aged 13 to 17 years recruited from high schools in the community of Madrid, Spain, prior to the initiation of alcohol use.

**Measurements:** We extracted measures of power spectral density and excitation–inhibition balance across the brain from MEG recordings and cognitive traits related to risk behaviors from a battery of self-report questionnaires. Alcohol consumption was evaluated during the follow-up visit through structured individual interviews.

**Findings:** Power-spectra in beta-band showed a positive correlation with alcohol use during both stages (baseline: rho = 0.33, $P < 0.05$; follow-up: rho = 0.35; $P < 0.05$) and a negative correlation with excitation–inhibition ratio (baseline: $P < 0.001$; rho = −0.56; follow-up: $P < 0.01$; rho = −0.37). Finally, biological sex showed strong moderation effect, where females drove the predictive relationship ($P < 0.001$; rho = 0.64; $\beta$ = −0,61).

**Conclusion:** Spontaneous electrophysiological brain activity may provide an early biomarker of future alcohol use in females and appears to be associated with activity profiles prone to inhibition.

KEYWORDS
adolescence, alcohol, electrophysiology, excitation–inhibition ratio, magnetoencephalography (MEG), puberty

## INTRODUCTION

Over the last two decades, animal studies, neuro-imaging research and behavioural investigations have established adolescence as a critical period for brain development, marked by significant changes in both brain structure and function [1] that promote higher-order and complex cognition [2, 3]. During this period, adolescents are particularly sensitive to rewarding effects, which may lead to risky behaviours such as substance misuse that impact on social, psychological and neurobiological development [4]. In this regard, researchers have demonstrated that alcohol use is linked to alterations in electrophysiological activity, such as increased theta and beta band power in frontal regions [5] and posterior occipitotemporal cortices [6, 7]. Similarly, functional connectivity studies have also highlighted disrupted resting-state networks associated with heavy drinking (HD) [8, 9]. However, there remains a critical need for prospective longitudinal studies to disentangle the neurobiological factors that predispose individuals to HD from those that result from alcohol consumption [10, 11]. Notably, no studies to date have characterised spontaneous power spectra in relation to the onset of alcohol use during adolescent brain development.

The onset of puberty involves several neurobiological changes that leave a distinctive fingerprint on spontaneous electrophysiological activity [12, 13]. During normative development, synaptic pruning and interneuron maturation in the brain [14–16] lead to faster power spectral density oscillations, particularly in the alpha, beta and gamma bands [17–20]. However, internal factors such as sex hormones have a critical role, causing significant sexual dimorphism in neurological maturation [21, 22]. In males, cortical maturation influenced by testosterone occurs gradually over a prolonged period of time. In contrast, puberty in females begins earlier and progresses faster owing to earlier increases in oestradiol [23–25], with a more pronounced increase in beta-band activity [18, 19]. In turn, recent studies, such as that published by McSweeney *et al*. (2021) [26], have also demonstrated sex-dependent maturation in aperiodic brain activity, an index of the excitatory/inhibitory (E/I) balance. This differential brain maturation arising from sex-related factors further influences the reward system, potentially shaping the development of substance consumption habits. In males, testosterone targets the nucleus accumbens, promoting risk-taking behaviours [27, 28], whereas in females, oestradiol amplifies dopaminergic release, leading to heightened vulnerability to the rewarding effects of substances [28–30].

This prospective longitudinal study aims to disentangle the neurobiological factors that predispose adolescents to HD from those arising from alcohol use itself. We hypothesise that specific electrophysiological differences in resting-state power spectra, previously observed in young adults engaging in binge drinking, are present prior to alcohol initiation and may serve as biomarkers of vulnerability. Furthermore, we investigate whether these differences reflect alterations in the excitation–inhibition balance and whether biological sex moderates these associations. To address these aims, we conducted three primary analyses within a longitudinal framework: (i) characterisation of power-spectra profiles related to alcohol use; (ii) correlation between electrophysiological profiles and the functional excitation–inhibition ratio (*fE/I*); and (iii) moderation of the brain activity–alcohol use relationship by biological sex. The primary research question and analysis plan were not pre-registered; therefore, the analyses should be considered exploratory.

## METHODS

### Participants

The participants were recruited from two projects funded by the Spanish Ministry of Health in 2015 and 2019. Participants were recruited at 13–17 years of age from different high schools across the community of Madrid, following an identical evaluation protocol in two stages separated by a 2-year follow-up period. Participants were screened to ensure no history of alcohol consumption, family alcohol use and psychiatric or neurological disorders. All participants completed the Alcohol Use Disorder Identification Test (AUDIT) [31] and a semi-structured interview regarding substance use habits. In the baseline visit, before the onset of alcohol use, 148 adolescents participated in a magnetoencephalography (MEG) recording for a period of 5 minutes in resting state with their eyes closed. A total of 114 of those participants also underwent magnetic resonance imaging (MRI). After the 2-year follow-up period, 73 participants were re-evaluated. Based on the AUDIT and interview information, we calculated the quantity of standard alcohol units (SAUs) (1 SAU = 10 mg ethanol) consumed during regular drinking episodes, considering the number and type of beverages consumed within 2–3 hours. Tobacco and cannabis use were also monitored, and those reporting regular consumption during the baseline visit were excluded [2]. After quality control of the MEG and MRI data, a final sample of 56 subjects (32 males and 24 females) completed the protocol. Informed consent was obtained from all participants and their parents or legal guardians in accordance with the Declaration of Helsinki, and the study received ethical approval from the ethics committee of the Universidad Complutense de Madrid. To rule out potential differences between participants who remained in the study ($n$ = 73) and those who dropped out ($n$ = 41), we conducted statistical comparisons on sex, age, alcohol use and self-reported questionnaire scores. The only significant difference was found in sex distribution, with a higher proportion of females in the dropout group (Appendix S1).

### Self-reported questionnaires

We used self-report scales to evaluate the following traits: Barratt Impulsiveness Scale, (BIS_11) [32]; Sensation Seeking Scale (SSS_V) [33]; Barkley Deficits in Executive Functioning Scale (BDEFS) [34]; Behavior Rating Inventory of Executive Function (BRIEF) [35]; and the Dysexecutive Questionnaire (DEX) [36]. These scales were administered during the recruitment stage within a larger sample of 838 participants. At the 2-year follow-up, all but nine

individuals from the sample used in this study were successfully contacted. Missing data for these participants were imputed using regression-based imputation, with the scales scores of the remaining 828 subjects serving as predictors. Descriptive statistics were examined for both the imputed values and the updated database including these cases. This inspection ensured that no outliers or deviations from the overall sample distribution were introduced by the imputation procedure. To reduce the dimensionality of the executive function questionnaires, we conducted a principal component analysis (PCA) using scores from BDEFS, BRIEF and DEX. This analysis yielded a single executive function component that accounted for 89.9% and 89.6% of the total variance across the questionnaires at baseline and at the 2-year follow-up, respectively.

## MRI recordings and volumetry

High-resolution 3D T1-weighted brain MRI scans were obtained at either the Santa Elena Foundation (GE Optima MR450w, 1.5 T; General Electric, Boston, MA, USA) or the Clinical Hospital of Madrid (GE Signa HDxt, 1.5 T; General Electric). The scan parameters for both machines included: echo time = 4.2 ms, repetition time = 11.2 ms, inversion time = 450 ms, field of view = 100, acquisition matrix = 256 × 256 and slice thickness = 1 mm.

## MEG recordings

MEG data were acquired using a 306-channel (102 magnetometers and 204 planar gradiometers) whole-head Elekta Neuromag system located in a magnetically shielded room at the Centre for Biomedical Technology in Madrid, Spain. Brain activity was recorded during an eyes-closed resting state using an online finite impulse response (FIR)-type anti-alias filter with a frequency range of 0.1–330 Hz and a sampling rate of 1000 Hz. The head shape of each participant was captured using a Fastrak digitiser (Polhemus, Colchester, VT, USA) with three fiducial landmarks (nasion and left and right pre-auricular points). Four head position indicator (HPI) coils were attached to the participant's scalp to track head position. Additionally, two sets of bipolar electrodes were used to monitor eye blinks and heartbeats.

## Signal processing and source–space reconstruction

To reduce environmental noise and correct for subject movements, a temporal extension of the signal space separation (tSSS) method was applied [37]. Fieldtrip [38] in MATLAB R2020b (MathWorks, Natick, MA, USA) was used to automatically detect artifacts in the MEG signal, which were then visually confirmed by an MEG expert and the artifact-free data were then segmented into 4-second epochs with two additional seconds of real data on either side as padding.

Individual MEG signals were estimated at the source level using the participant's T1-weighted MRI with a homogeneous grid based on the Automated Anatomical Labeling (AAL) atlas [39]. This grid comprised 1202 positions corresponding to 78 cortical regions, which were transformed into the participant's space using a linear transformation between the Montreal Neurological Institute (MNI) template and the participant's T1-weighted MRI. Additionally, the T1-weighted image was employed to create a single-shell head model based on the inner surface of the skull [40]. Finally, a linearly constrained minimum variance (LCMV) beamformer was applied as the inverse method to reconstruct the signal in the cortical sources.

## Analysis 1: characterization of power-spectra profiles related to alcohol use

To identify the brain activity profiles associated with alcohol use, we considered previous findings in the literature reporting increased activity in the brains of heavy alcohol users. Based on this hypothesis, we performed an exploratory analysis of the positive correlations between alcohol consumption and spectral power across different frequency bands in each of the 1202 cortical nodes, and then used the cluster-based permutation test (CBPT) implemented in Fieldtrip [38, 41] to correct for multiple comparisons.

### Power spectra calculations

The power spectrum at each source was computed using the Fieldtrip toolbox [38] and a multi-taper method (mtmfft) with discrete prolate spheroidal sequences (dpss) as the windowing function and 1-Hz smoothing. We analysed relative power by normalising each frequency step by the total power across the entire spectrum in the range of 2–45 Hz. This resulted in a source-reconstructed matrix with dimensions of 1202 nodes × 173 frequency steps × 55 participants. To further investigate whether activity in these frontal regions changed meaningfully over time, we computed the parametrised symmetric change in power ($POW_{change}$) using the following formula:

$$POW_{change}(\%) = \frac{(POW_1 - POW_0)}{\left(\frac{POW_1 + POW_0}{2}\right)(t_1 - t_0)} * 100$$

### Cluster-based permutation test (CBPT)

To assess possible associations between SAUs and classical bands normalised power (theta = 4–8 Hz, alpha = 8–12 Hz, low beta = 12–20 Hz, high beta = 20–30 Hz and gamma = 30–45 Hz) or parametrised symmetric changes in power, a CBPT approach was used. For each of the 1202 grid nodes, right-tailed Spearman's partial correlation tests were performed, controlling for age, sex and project. Significant clusters were identified by detecting spatially adjacent nodes that exhibited a partial correlation with $P < 0.05$. To qualify as a candidate cluster, it had to comprise at least 1% of the total nodes (i.e. 12 nodes) and demonstrate significance across a minimum of three

consecutive frequency bands. Subsequently, the Spearman's *rho*-values were transformed into Fisher's *Z*-values. The cluster-mass statistic was then computed as the sum of the *Z*-values for all nodes within each cluster. To control for multiple comparisons, the statistical analysis was repeated 50 000 times with shuffled data to generate a maximal null distribution. This empirical distribution allowed us to calculate the *P*-value corresponding to each of the original candidate clusters. Finally, clusters with a CBPT *P*-value of <0.05 were selected for further analysis. To correct the results for the effect of impulsivity, CBPT analyses were repeated using the BIS_11 scores as a covariate. To ensure consistency and reduce the number of comparisons in subsequent models, we averaged the spectral power across both the spatial and frequency dimensions to obtain a representative metric of the identified electrophysiological pattern.

## Analysis 2: correlation between electrophysiological profiles and functional excitation–inhibition ratio (*fE/I*)

### Functional excitation–inhibition ratio

To estimate *fE/I*, we applied the algorithm developed by Bruining *et al.* (2020) [42], which provides a functional measure of the *E/I* ratio from ongoing electrophysiological recordings. Before applying the algorithm, the segmented source–space signals were converted into continuous time series by concatenating consecutive segments and interpolating across artifact-disconnected gaps, thereby maximising the length of the continuous data available for the analysis. The signal profile for each source was defined as the cumulative sum of the demeaned amplitude envelope, segmented into 5-second windows with 80% overlap. Each window was amplitude-normalised, detrended and its standard deviation calculated. *fE/I* values were estimated in 1202 sources within the low-beta band (12–20 Hz) using the Pearson correlation between windowed mean amplitudes and standard deviations. Interpretation: *fE/I* > 1 indicates excitation dominance, *fE/I* < 1 indicates inhibition dominance and *fE/I* = 1 indicates a balanced system. Detrended fluctuation analysis (DFA) was applied, and mean *fE/I* values per participant were averaged across CBPT clusters with DFA exponents of >0.55 to exclude unreliable values.

### Statistical analysis: partial correlation and linear regression

To analyse the association between the physiological traits obtained in analysis 1, SAUs and levels of *fE/I*, Spearman's partial correlations, were calculated for each stage of the study, controlling for the effects of sex, age and project. To assess the shared variance explained by beta-band power and *E/I* levels on alcohol consumption, we performed a stepwise linear regression analysis. In this model, alcohol consumption was set as the dependent variable, while beta power and the *E/I* ratio served as predictors.

## Analysis 3: moderation of the brain activity–alcohol use relationship by biological sex

### Statistical analysis: moderation

Moderation effects were assessed using the Statistical Package for the Social Sciences (SPSS) 29.0.2.0 and the macro *Process 4.3* [43] (www.processmacro.org/index.html). The relative power of the cluster and *fE/I* were used as predictors, the SAUs were used as the dependent variable and sex was used as a moderator. In addition, age was included as a covariate to eliminate its effect on the analysis.

# RESULTS

## Demographics

After the follow-up period, adolescents had an average alcohol consumption of 3.9 ± 2.6 SAUs, with no significant difference between males and females. Regarding behavioural variables, differences were shown in sensation seeking during the baseline visit (*P* = 0.01), where males had higher scores on the SSS_V questionnaire (20.8 ± 6.0) compared with their female counterparts (16.6 ± 5.5). The means and standard deviations of the whole sample and both sexes as well as the differences between groups are detailed in Table 1.

## Experiment 1: power spectra related to alcohol use

### Pre-consumption MEG

The CBPT analysis reveals a positive correlation between future alcohol consumption and spectral power between 12 and 19.75 Hz (Figure 1). At lower frequencies, the cluster encompasses the bilateral temporal lobes, then expands with increasing frequency to the occipital and frontal regions, to finally be reduced to a few frontal and occipital sources at higher frequencies. Spearman's *rho* ranged between 0.23 and 0.42, with an averaged statistical parameter of *P* = 0.045 and *rho* = 0.33. No significant differences were found in the rest of the bands analysed. Once controlled for the effects of the BIS_11 score, significance was preserved, and the spatial and spectral distributions of the cluster were maintained (Appendix S2).

### Post-consumption MEG

Two years later, CBPT analysis reveals a positive correlation between power and SAUs (CBPT *P* = 0.048, *rho* = 0.35) between 12 and 19.75 Hz (Figure 2) with Spearman's *rho* ranging between 0.23 and 0.49. At lower frequencies, the cluster was limited to the bilateral temporal regions, then extended toward occipital, parietal and inferior frontal regions, and finally was reduced to occipital sources at higher frequencies. No significant differences were found in the rest of the

**TABLE 1** Substance use, age and cognitive scale scores throughout the study and *t*-test comparison between sexes for each variable.

| | Whole *n* = 42 | Range | Male *n* = 32 | Female *n* = 24 | *t* | Cohen's *D* | *P* |
|---|---|---|---|---|---|---|---|
| Baseline visit | | | | | | | |
| Age | 14.4 (0.6) | 13.3, 17.0 | 14.5 (0.7) | 14.4 (0.6) | 0.73 | 0.65 | 0.47 |
| SSS_V | 19.0 (6.1) | 6, 32 | 20.8 (6.0) | 16.6 (5.5) | 2.66 | 5.79 | 0.01* |
| BIS_11 | 49.1 (13.9) | 25, 94 | 49.8 (15.2) | 48.1 (12.0) | 0.45 | 13.96 | 0.66 |
| PCA_exe | 0.0 (25.3) | −48.4, 54.2 | −2.0 (31.0) | 2.7 (24.5) | −0.61 | 28.42 | 0.54 |
| 2-year follow-up | | | | | | | |
| Age | 16.4 (0.6) | 15.4, 18.9 | 16.5 (0.7) | 16.3 (0.6) | 0.59 | 0.63 | 0.38 |
| SSS_V | 21.32 (4.7) | 9, 31 | 21.8 (4.9) | 20.7 (4.5) | 0.89 | 4.75 | 0.38 |
| BIS_11 | 48.8 (14.0) | 21, 73 | 49.2 (14.3) | 48.3 (13.8) | 0.25 | 14.11 | 0.80 |
| PCA_exe | 0 (22.3) | −49.6, 54.2 | −3.8 (21.45) | 5.1 (22.9) | −1.5 | 22.06 | 0,14 |
| SAUs | 4.0 (2.6) | 0, 8 | 3.9 (2.6) | 4.1 (2.8) | −0.35 | 2.66 | 0.73 |
| Tobacco | 4/56 | – | 1/32 | 3/24 | – | – | – |
| Cannabis | 2/56 | – | 0/32 | 2/24 | – | – | – |

Abbreviations: SSS_V, Sensation Seeking Scale; BIS_11, Barrat Impulsiveness Scale; PCA_exe, 1st principal component of executive questionnaires; SAUs, standard alcohol units.
*Significant difference between males and females.

bands analysed. Once controlled for the effects of the BIS_11 score, significance was preserved, and the spatial and spectral distributions of the cluster were maintained (Appendix S3). Finally, the CBPT analyses performed on the parametrised symmetric change of the power between stages did not reveal any significant results.

## Experiment 2: greater low-beta power is associated with lower *fE/I* values

The mean duration of the time series was 281.74 s and surpassed 180.25 s in all cases. After correcting the *fE/I* values by the DFA exponents, an average of 80.38% of the sources were marked as reliable during the baseline visit of the study, with 88.49% marked as reliable during the 2-year follow-up, constituting a representative measure of the excitation–inhibition balance. Once calculated, the *fE/I* values were correlated with the cluster power obtained in the baseline visit, revealing a significant negative association ($P < 0.001$, Spearman's *rho* = −0.56) (Figure 3). In addition, *fE/I* values during the baseline visit also showed a positive correlation with future consumption ($P = 0.01$, Spearman's *rho* = −0.35). The stepwise linear regression analysis revealed that, although both low-beta power and the *fE/I* ratio independently showed predictive capacity for alcohol consumption, a substantial portion of the explained variance was shared between them. As a result, the final regression model retained only the *fE/I* ratio as a significant predictor ($P < 0.05$, $r^2 = 0.12$, SE = 2.5). On the other hand, the association between low-beta power and *fE/I* was replicated during the follow-up ($P < 0.01$, Spearman's *rho* = −0.36) (Figure 3). However, no significant associations were found between alcohol consumption and *fE/I* during the follow-up visit.

## Experiment 3: sex moderates the relationship between power spectra and alcohol use

Moderation analysis revealed a significant interaction between sex and relative power during the baseline visit, where the significance of the prediction was relevant only in the female group ($P < 0.001$, Spearman's *rho* = 0.63). However, no moderating effects of sex on the *fE/I*–SAUs relationship were found. Moderation analyses during the 2-year follow-up found a predictive value of alcohol on relative power without any significant interaction with sex. A detailed description of the models is depicted in Table 2. The partial correlations between relative power and consumption in the whole sample and in each of the sexes can be found in Appendix S4.

# DISCUSSION

## Summary of the main findings

This study aimed to characterise the electrophysiological power spectra and excitation–inhibition balance associated with HD onset, and its impact on brain activity during adolescence. Additionally, we explored how biological sex moderates this association. Findings revealed that increased beta-band power in the frontal, temporal and parieto-occipital cortices was related to higher alcohol consumption 2 years later. A similar pattern emerged after drinking onset, with higher beta-band power linked to increased consumption rates. These electrophysiological features were associated with a lower *E/I* ratio and were strongly moderated by sex.

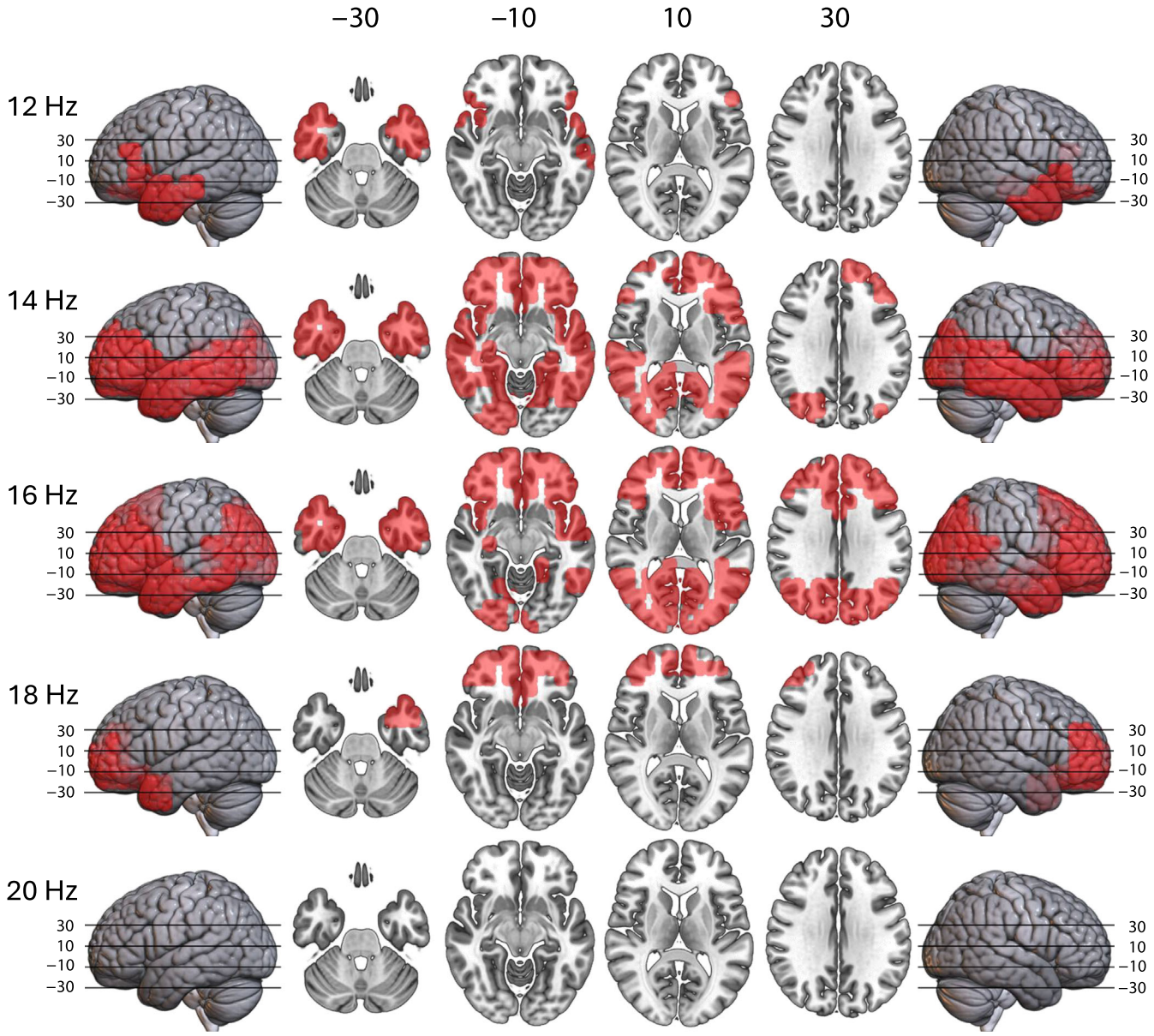


**FIGURE 1** Correlation between low-beta (12–20 Hz) spectral power during the baseline visit and future number of standard alcohol units (SAUs) consumed. The figure highlights the progression of cluster morphology (shaded in red) across frequency steps. Axial brain slices are presented in Montreal Neurological Institute (MNI) coordinates.

## Alterations in power caused by heavy alcohol consumption

Previous literature has reported that HD in young adults at university causes an increase in beta-band activity during resting-state lectroencephalography (EEG), particularly in frontal and temporal regions [4, 5, 7], and decreases at low frequencies [5, 44]. Such results were explained as a compensatory mechanism, according to which, the brain allocates higher resources to compensate for underlying neural deficits [6]. Notably, these alterations resemble those observed in alcohol-dependent individuals, suggesting that HD may share similar neurotoxic effects [45]. However, current results suggest that electrophysiological differences in the beta band exist prior to consumption and persist throughout adolescence following the initiation of alcohol use. This evidence aligns with prior findings that suggest the existence of functional connectivity profiles prone to consumption [10, 11]. However, no associations were found between alcohol consumption and alpha or theta power. This suggests that decreased slow-band power may result from prolonged consumption.

## Implications of excitation–inhibition balance in the beta band

Beta rhythm is widely recognised for its broad involvement in cognitive processes and brain dynamics [46–48]. During the resting state, it

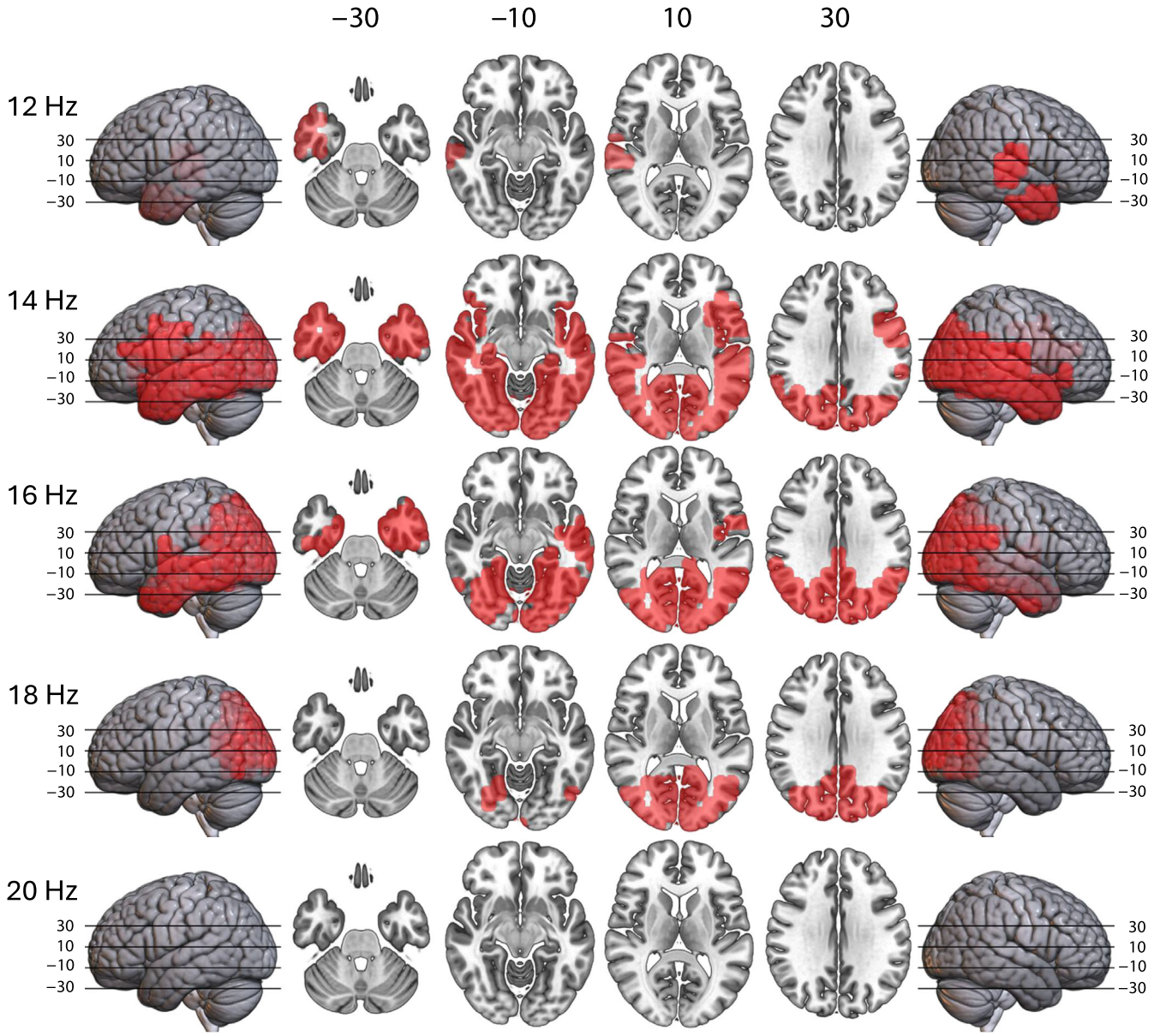


**FIGURE 2** Correlation between low-beta (12–20 Hz) spectral power during the 2-year follow-up and number of standard alcohol units (SAUs) consumed. The figure highlights the progression of cluster morphology (shaded in red) across frequency steps. Axial brain slices are presented in Montreal Neurological Institute (MNI) coordinates.

is proposed to facilitate the integration of resting-state networks and support the global efficiency of the brain [46]. On the other hand, excessive beta-band power has been associated with reduced cognitive flexibility, ruminative thoughts, compulsive behaviours [46, 47, 49] and addiction disorders [50]. In light of recent results, it has been proposed that increases in beta-band power reflect an excitatory–inhibitory imbalance potentially linked to alterations in the gamma-aminobutyric acid (GABA)ergic and glutamatergic neurotransmitter systems [5, 7, 51]. In accordance with these hypotheses, animal and human studies have shown that continued alcohol use causes a decrease in GABAa receptors and an excitatory upregulation [52, 53]. Conversely, in our results, increases in beta power were associated with a more inhibition-prone ratio. In this regard, during adolescent neural development changes in electrophysiological activity are a common phenomenon [54] owing to cortical circuitry transformations [55, 56]. This process is influenced by facilitating factors, such as synaptic pruning and the maturation of parvalbumin-positive (PV+) interneurons, which facilitated locally evoked activity and enhance neuronal plasticity [14–16]. Meanwhile, myelin development stabilises neural networks and increases transmission speed between cortical regions [14, 55, 57]. Taken together, these developmental changes promote shifts in electrophysiological activity towards faster-frequency bands, particularly in posterior regions and the pre-central gyrus [18, 20, 54]. Thus, differences prior to alcohol consumption may arise from divergent neurodevelopmental trajectories that modulate electrophysiological activity and may predispose some individuals to approach

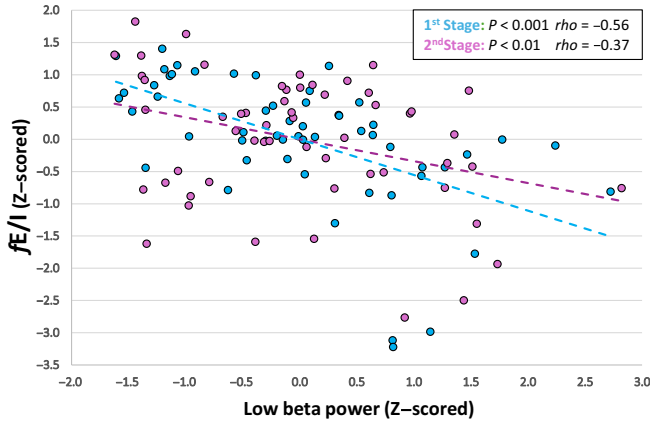


**FIGURE 3** Correlation between the power in the low beta band and the functional excitation–inhibition ratio (*fE/I*) in the clusters identified in the cluster-based permutation test (CBPT) analysis. The individual values and the regression line of the relationship for the baseline visit are shown in blue. The individual values and the regression line of the ratio for the 2-year follow-up are shown in purple.

**TABLE 2** Moderation analysis for sex in the prediction of standard alcohol units (SAUs) consumed.

| | β | SE | *t* | *P* |
|---|---|---|---|---|
| Baseline visit | | | | |
| Constant | 3.90 | 2.84 | 1.38 | 0.17 |
| Low beta power (*Z*-scored) | 0.64 | 0.18 | 3.58 | <0.001 |
| Sex | 0.02 | 0.25 | 0.08 | 0.93 |
| Sex * low beta power | −0.61 | 0.25 | −2.41 | 0.02 |
| Age | −0.27 | 0.19 | −1.39 | 0.17 |
| Conditional effects | | | | |
| Females | 0.64 | 0.18 | 3.58 | <0.001 |
| Males | 0.03 | 0.18 | 0.18 | 0.86 |
| 2-year follow-up | | | | |
| Constant | 3.17 | 3.49 | 0.91 | 0.37 |
| Low beta power (*Z*-scored) | 0.43 | 0.18 | 2.38 | 0,02 |
| Sex | 0.07 | 0.27 | 0.28 | 0.78 |
| Sex * low beta power | −0.12 | 0.27 | −0.46 | 0.65 |
| Age | −0.20 | 0.21 | −0.92 | 0.36 |

substance use in a riskier way [58, 59]. Interestingly, the increases in beta-band power and the reduction in the inhibition–excitation index described in this study may resemble an early pseudomaturation state, previously noted in the literature as a risk profile [11, 60].

## Influence of sex on neurodevelopment and alcohol initiation

Once puberty begins, a cascade of neuroanatomical and functional changes occurs, resulting in sexual dimorphism, which is consistently reported in the literature [22, 23, 61]. Current findings align with this framework, indicating that the association between alcohol consumption and electrophysiology shows a differential relationship according to sex. In this scenario, females with prominently inhibitory cortical activity would present a higher level of alcohol consumption, possibly linked to early pseudomaturation processes that facilitate reward-seeking and risk-taking behaviours, such as alcohol misuse. To our knowledge, no prior studies have specifically explored sex differences in electrophysiology at pre-consumption stages. However, a recent review by Almeida-Antunes *et al.* (2021) [6] indicated that studies with heavy drinkers at university do not detect consistent electrophysiological differences between the sexes. These findings are consistent with the follow-up of our study, where the moderating effect of sex on the beta–consumption relationship disappeared 2 years later. This phenomenon may be attributed to the asynchrony of the maturation trajectories between males and females, which tends to converge during this period [22]. On the other hand, our results may stem from varying factors underlying alcohol use between the sexes. In males, higher levels of sensation-seeking, likely driven by peak testosterone levels during adolescence, appear to promote consumption behaviours [62]. In contrast, consumption in females seems linked to earlier and distinct maturational changes at the structural and physiological level, potentially influenced by oestradiol effects on their nervous system.

## Strengths and limitations

The current study has several limitations that should be addressed in future research. First, although our results align with the hypothesis of pubertal differences, we lacked specific measures of pubertal stage in our sample. This information is crucial given current evidence and should be collected in future studies. Second, the study collected data at two time points—early and mid-adolescence. While this is sufficient to identify predisposition factors and its evolution, incorporating a third time point in late adolescence would allow for a more precise characterisation of the electrophysiological maturation. Another limitation of this study is the sample size, which may restrict the generalisability of the findings. However, this constraint is common in longitudinal neuroimaging research, particularly when involving resource-intensive techniques such as MEG. Finally, as noted by the original authors of the CBPT method [41], this approach is designed to test whether significant effects exist, not to ensure the direct comparability between spatial clusters across conditions or timepoints. The distribution of a cluster might be informative about where an effect is mostly concentrated, but differences in cluster locations between stages may reflect differences in statistical detectability rather than true biological divergence. For these reasons, although the apparent disappearance of frontal effects after alcohol onset is noteworthy, further work with larger samples and dedicated designs will be needed to confirm whether these differences reflect meaningful neurodevelopmental changes related to alcohol use. Nonetheless, the strength of this study lies in its longitudinal approach, utilising robust and cutting-edge methodologies to explore the electrophysiological phenotypes associated with adolescent alcohol consumption.

## CONCLUSION

In conclusion, spontaneous electrophysiological activity may represent an early biomarker of alcohol consumption initiation years later and is related to the appearance of excitation–inhibition imbalance. Contrary to cross-sectional studies in young binge drinkers, some of this trait arises form maturational changes rather than the effects of alcohol drinking itself. Moreover, this predisposition towards the initiation of alcohol consumption shows a sex-dependent impact in adolescence behaviours. These differences show distinctive physiological and psychological correlates for males and females, which should be further explored. For this reason, the development of preventive strategies should consider these individual factors to efficiently investigate the needs and motivations of young people.

### AUTHOR CONTRIBUTIONS

**Alberto del Cerro-León:** Data curation (lead); formal analysis (lead); investigation (supporting); methodology (lead); software (lead); writing—original draft (lead). **Marcos Uceta:** Data curation (supporting); formal analysis (supporting); investigation (supporting); writing—review and editing (supporting). **Danylyna Shpakivska-Bilan:** Data curation (supporting); formal analysis (supporting); methodology (supporting); writing—review and editing (supporting). **Isabel Suárez-Méndez:** Methodology (supporting); resources (supporting); software (supporting); writing—review and editing (supporting). **Héctor Peribáñez-Baz:** Data curation (supporting); formal analysis (supporting); writing—review and editing (supporting). **Pablo Cuesta:** Formal analysis (supporting); investigation (supporting); methodology (lead); resources (supporting); software (equal); writing—review and editing (supporting). **Ricardo Bruña:** Formal analysis (supporting); investigation (supporting); methodology (equal); software (lead); writing—review and editing (supporting). **Luis M. García-Moreno:** Conceptualization (equal); funding acquisition (lead); investigation (equal); project administration (lead). **Fernando Maestú:** Conceptualization (lead); funding acquisition (lead); investigation (lead); project administration (lead); supervision (supporting); writing—review and editing (supporting). **Luis Fernando Antón-Toro:** Conceptualization (lead); data curation (equal); formal analysis (supporting); investigation (lead); methodology (supporting); project administration (supporting); supervision (lead); writing—review and editing (lead).

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### DECLARATION OF INTERESTS

All authors report no biomedical financial interests or potential conflicts of interest.

### DATA AVAILABILITY STATEMENT

Processed data for power and *fE/I* and scripts for statistics are publicly available on the Open Science Framework (OSF) website (https://osf.io/dtb2u/). Raw data can be accessed through a data transfer agreement with the responsible university (Universidad Complutense de Madrid). Finally, the MEG signal pre-processing and cleaning codes can be found publicly available on the GitHub repository (https://github.com/rbruna/meeg_analysis).

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