





# Electrophysiological resting-state hyperconnectivity and poorer behavioural regulation as predisposing profiles of adolescent binge drinking

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## Abstract

Adolescent Binge Drinking (BD) has become an increasing health and social concern, with detrimental consequences for brain development and functional integrity. However, research on neurophysiological and neuropsychological traits predisposing to BD are limited at this time. In this work, we conducted a 2-year longitudinal magnetoencephalography (MEG) study over a cohort of initially alcohol-naïve adolescents with the purpose of exploring anomalies in resting-state electrophysiological networks, impulsivity, sensation-seeking, and dysexecutive behaviour able to predict future BD patterns. In a sample of 67 alcohol-naïve adolescents (age =  $14.5 \pm 0.9$ ), we measured resting-state activity using MEG. Additionally, we evaluated their neuropsychological traits using self-report ecological scales (BIS-11, SSS-V, BDEFS, BRIEF-SR and DEX). In a second evaluation, 2 years later, we measured participant's alcohol consumption, sub-dividing the original sample in two groups: future binge drinkers (22 individuals, age  $14.6 \pm 0.8$ ; eight females) and future light/no drinkers (17 individuals, age  $14.5 \pm 0.8$ ; eight females). Then, we searched for differences pre-dating alcohol BD intake. We found abnormalities in MEG resting state, in a form of gamma band hyperconnectivity, in those adolescents who transitioned into BD years later. Furthermore, they showed higher impulsivity, dysexecutive behaviours and sensation seeking, positively correlated with functional connectivity (FC). Sensation seeking and impulsivity mainly predicted BD severity in the future, while the relationship between dysexecutive trait and FC with future BD was mediated by sensation seeking. These findings shed light to electrophysiological and neuropsychological traits of vulnerability towards alcohol consumption. We hypothesise that these differences may rely on divergent neurobiological development of inhibitory neuro-transmission pathways and executive prefrontal circuits.

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## KEYWORDS

binge drinking, executive functions, functional connectivity, magnetoencephalography, resting state, sensation seeking

## 1 | INTRODUCTION

Binge Drinking (BD) has become an extended pattern of alcohol consumption among adolescents related to many health and social disturbances.<sup>1</sup> It is characterised by the intake of at least four (for women) or five (for men) standard alcohol units (SAUs) in a short interval of time.<sup>1</sup> Such a pattern of alcohol misuse is particularly hazardous during adolescent neurodevelopment.<sup>2,3</sup> It causes substantial alterations in the brain's integrity, for example, in structural<sup>4,5</sup> and functional aspects,<sup>6–9</sup> as well as neuropsychological alterations,<sup>10</sup> and could also increase psychological traits such impulsivity and disinhibited sensation seeking.<sup>10</sup>

However, the cross-sectional nature of the aforementioned works does not allow for making assumptions regarding predisposition factors that could make some individuals prone to engage in alcohol misuse. In this sense, some authors have proposed that particular profiles, characterised by higher impulsivity, sensation seeking, and dysexecutive behaviours, may play a predisposition role in the development of such habits.<sup>11</sup> In this regard, some of the neurobiological changes that coincide with puberty result in a desynchronisation between the maturation of subcortical regions (i.e. brain reward system) and later, cortical regions (prefrontal control systems).<sup>12</sup> These changes are related to increases in sensation-seeking and impulsivity profiles, promoting the search for reinforcing substances such as alcohol, and linked in turn to lower cognitive control abilities needed to control maladaptive behaviours.<sup>13,14</sup> However, although these characteristics are typical of adolescents, they are not present in all individuals equally, being accentuated in those adolescents that will develop higher alcohol intake.<sup>13,14</sup>

However, studies evidencing the neurobiological counterpart of those profiles are scarce at this time. An increasing number of studies have outlined differences in brain structure and hemodynamical functioning<sup>15,16</sup> linked to future alcohol use. Furthermore, understanding the complex mechanism that governs these challenging behaviours would require the study of large-scale brain functional interactions under the scope of functional networks.<sup>17</sup>

Magnetoencephalography (MEG) provides an optimal balance of spatial and temporal resolution when studying neurophysiological activity networks.<sup>18</sup> The study of the functional connectivity (FC) – defined as the existence of statistical dependencies between the time series of two or more brain regions<sup>19</sup> – may reveal important information regarding the integrity and efficiency of functional networks.<sup>20,21</sup> The resting-state networks, based on the measure of synchronisation in spontaneous and task-free oscillatory activity,<sup>22</sup> are able to manifest neurophysiological abnormalities regarding diverse brain states,<sup>18</sup> including alcohol use disorders (AUDs) and BD-related alterations.

In this vein, only a few studies evidenced abnormal resting-state connectivity related to BD in college students<sup>6,23</sup> and in association with the development of subsequent BD problems.<sup>24,25</sup> In general

terms, after BD onset, those studies reported patterns of cortical hypersynchronisation, while predating BD, some functional magnetic resonance imaging (fMRI) studies reported cortical hyperconnectivity<sup>24</sup> and reduced cortico-subcortical connectivity.<sup>25</sup> Nonetheless, despite the important evidence provided by those studies, it remains unknown how BD predisposing profiles may be depicted by cortical electrophysiological dynamics. To our knowledge, only one MEG work explored this matter experimentally in relation to inhibitory control (IC) processes.<sup>26</sup> However, it is not entirely clear whether such abnormal connectivity is dependent of a particular set of cognitive processes (i.e. executive functions) or relies on deeper neurobiological features.

Therefore, the aim of the present work is to characterise the baseline cognitive and electrophysiological predisposition profiles in the future development of BD behaviours. For that purpose, we carried out a longitudinal study over a cohort of initially alcohol-naïve adolescents. We measured their neuropsychological traits by ecological self-reported scales, while their electrophysiological FC was measured by MEG resting-state recordings. After a 2-year follow-up period, differences prior to alcohol intake were analysed between adolescents who became binge drinkers and those who remained abstainers or very light drinkers. Additionally, we aimed to explore which neuropsychological and electrophysiological factors would be most predictive of future consumption severity. From this standpoint, we hypothesise that future BDs will show patterns of increased FC prior to the onset of alcohol BD. This abnormal connectivity would involve regions primarily involved in adolescent cortical neuro-maturation, such as medial and lateral prefrontal cortex (PFC), parietal, and medial temporal structures.<sup>27</sup> Furthermore, based on previous work (Antón-Toro et al, 2021), we hypothesise that resting-state hypersynchronisation would occur predominantly in the fast frequency bands (such as alpha, beta and gamma bands). Along with functional anomalies, we expect higher profiles of impulsivity, dysexecutive behaviours and uninhibited sensation seeking. Finally, we will explore the relationship between electrophysiological, neuropsychological variables and future BD behaviours. To our knowledge, this is the first study to address resting-state neurophysiological networks in relation to BD predisposition, providing an important step forward in the detection of neurofunctional risk factors associated with the development of substances misuse.

## 2 | METHODS AND MATERIALS

### 2.1 | Participants

A total of 67 right-handed participants (mean age = 14.5 ± 0.9) with no family history of AUD, neurological or psychiatric disorders, and no

previous reports of alcohol consumption, measured by the Alcohol Use Disorders Identification Test (AUDIT), were recruited from different educational centers in the region of Madrid. All participants completed a longitudinal study with two stages of assessment, with a 2-year follow-up period between both assessments. At the end of the study, 39 of the 67 participants were used for the analysis. The participants and their legal guardians signed an informed consent form at each stage of the study, in accordance with the declaration of Helsinki and approved by the ethical committee of the Complutense University of Madrid.

## 2.2 | MEG acquisition

MEG data were acquired using a 306-channel Elekta Neuromag system located in the Center for Biomedical Technology (Madrid, Spain), using an online anti-alias filter between 0.1 and 330 Hz and a 1000 Hz sampling rate. Environmental noise was reduced offline using the temporal extension of the signal space separation method,<sup>28</sup> using the software Maxfilter (v 2.2 Elekta AB, Stockholm, Sweden), and subject movements were compensated using the same algorithm. We used FieldTrip package<sup>29</sup> in MatLab environment, for artifact inspection and removal. Finally, the acquired data were segmented into 4-s epochs of artifact-free data. The procedure is extensively detailed in the “supporting information materials and methods”.

## 2.3 | MRI acquisition

A General Electric Optima MR450w 1.5 T machine was used to obtain structural magnetic resonance imaging (MRI) data. Imaging protocol consisted in 3D T1-weighted high-resolution images with parameters: TE = 4.2 ms, TR = 11.2 ms and TI = 450 ms; flip angle = 12°, FoV = 100; acquisition matrix = 256 × 256 and slice thickness = 1 mm.

## 2.4 | Neuropsychological scales

We selected widely used scales to assess traits of impulsivity, sensation seeking and dysexecutive behaviours in a highly ecological way by means of self-report scales of daily life behaviours. First, the Barratt impulsivity scale (BIS-11, Martínez-Loredo et al, 2015<sup>30</sup>) consists of 30 items to measure impulsive personality traits. Secondly, the sensation-seeking scale (SSS-V; Zuckerman, 2007<sup>31</sup>) consists of 40 dichotomous items assessing four dimensions: thrill and adventure seeking, disinhibition, experience seeking and susceptibility to boredom. The disinhibition scale is of particular interest in this work, as it reflects the tendency to experience risky behaviours. Finally, we choose three different scales to inform regarding dysexecutive behaviours, as they focus on different aspects and behaviours related with executive dysfunction: the Barkley deficits of executive function scale (BDEFS; Barkley, 2012<sup>32</sup>) in its abbreviated version, consisting of 20 items, which assesses symptoms of

the PFC dis-executive syndrome associated with activities of daily living. The behaviour rating inventory of executive function (BRIEF-SR, adolescent's version; Gioia et al, 2010<sup>33</sup>), consisting of 89 items, which evaluates a wide spectrum of dysexecutive behaviours, classified into two general subscales (behavioural regulation index and metacognitive index). The dysexecutive questionnaire (DEX; Pedrero Pérez et al, 2009<sup>34</sup>) consists of 20 items for the evaluation of frontal dysfunctions.

## 2.5 | Procedure

In a first stage, all participants were assessed using an ecological battery of self-report scales for the assessment of daily life behaviours in the traits of impulsivity (BIS-11), sensation seeking (SSS-V) and dis-executive behaviours (BDEFS, BRIEF-SR and DEX), as well as their alcohol consumption habits using the AUDIT questionnaire. The electrophysiological activity was obtained by MEG recording in the resting state with eyes closed and brain structure by individual MRI.

Two years later, 53 participants completed the second phase of the assessment protocol, which included a comprehensive measurement of BD patterns using the AUDIT questionnaire and a semi-structured interview. During this interview, each participant was asked about the existence of drinking episodes during the 2-year follow-up phase. If the response was affirmative, they were asked to detail as precisely as possible a “typical” drinking episode during the last 6 months (i.e. amount of consumption, type of drink, hours of duration of the episode and the number of episodes in the last year). Based on this information, the participants were divided into two groups: a group of future BD consumers (fBD), with a drinking pattern of 4/5 (women/men) or more SAUs per session; and a group with those participants who remained abstainers or with a very light consumption (fLD), with 2 or less SAUs per session. Those participants with intermediate alcohol consumption, incomplete drinking assessment or poor MEG signal quality, were discarded from the final sample (14 participants). Thus, the final sample consisted of 22 fBD (mean age = 14.19 ± 0.65; 9 females; mean UBEs = 5.77 ± 1.69) and 17 fLD (mean age = 14.18 ± 0.88; 8 females; mean UBEs = 1.02 ± 0.94).

## 2.6 | Source-space reconstruction

MEG data were transformed to source space using a realistic single shell<sup>35</sup> generated from the individual T1 image in SPM12 as forward model and a linearly constrain, minimum variance beamformer as inverse model.<sup>36</sup> The data were reconstructed into 2459 source positions located inside the cranial cavity. These source positions were labelled according to the Automated Anatomical Labelling atlas (AAL),<sup>37</sup> and only the 1188 positions labelled as 1 of 76 cortical areas were considered. We reconstructed each source independently for each classical band: theta (4 to 8 Hz), alpha (8 to 12 Hz), low beta (12 to 20 Hz), high beta (20 to 30 Hz) and low gamma

(30 to 45 Hz). For this, we filtered the data using a finite impulse response filter of 1800th order designed using a Hann window, adding 2 s of real data at each side as padding. Last, we used the epoch-averaged covariance matrix to build the adaptive spatial filter.

## 2.7 | FC analysis

The FC was estimated under the hypothesis of phase synchronisation using the phase locking value (PLV)<sup>38</sup> over segments of 4 s of duration. In the first step, the PLV was calculated separately for each pair of source positions, generating an FC matrix of 1188 by 1188. Then, we performed a study of the functional synchronisation between all cortical regions of interest (ROIs) predefined by the AAL<sup>39</sup> through a ROI-based synchronisation analysis. To do so, we calculated the root-mean-square of PLV values of all links connecting each pair of cortical areas of the AAL atlas, generating a 76 by 76 whole-brain FC matrix.

## 2.8 | Statistical analysis

In a first step, we compared the PLV values between each pair of ROIs in both groups using an analysis of covariance (ANCOVA) test with age and sex as covariates. The resulting *p* values were corrected for multiple comparisons using a false discovery rate (FDR<sup>40</sup> of 10%, and for source leakage bias using the correlation of spatial filters as covariate; see “supporting information”). In the next step, for those links that resulted significant, we calculated the principal components of connectivity links using a *principal component analysis* (PCA) (Jolliffe and Morgan, 1992). Regarding neuropsychological scales, we used

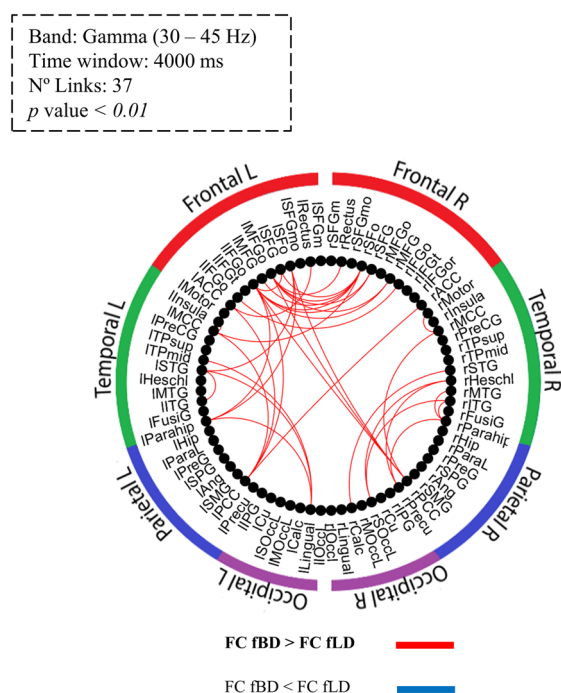
PCA to calculate the principal dysexecutive component (EXE-pca1) from the scores of the three dysexecutive scales (BDEFS, BRIEF and DEX). From this point, first, we performed a between-group ANCOVA comparison for BIS-11, SSS-V and EXE-PCA1 scores, as well as PLV components (PLV-pca1 and PLV-pca2), using sex and age as covariates.

Next, we explored the correlation between FC components (PLV-pca1 and PLV-pca2), together with neuropsychological traits (EXE-pca1, BIS-11 and SSS-V) and alcohol consumption ratio (number of SAUs), by means of one-tailed Spearman's correlation. Those variables with a significant correlation were then introduced in a multivariate stepwise regression model, in order to depict which factors were more predictive of alcohol consumption. Lastly, as a post-hoc analysis, we conducted a mediation analysis<sup>41</sup> to explore the relationship between these predictive variables and those that showed between-group differences but were not able to predict future BD.

## 3 | RESULTS

### 3.1 | Functional connectivity

The FC analysis showed a pattern of hyperconnectivity in the fBD group in the gamma frequency band when compared to the fLD group. After FDR correction and suppression of source leakage bias, 37 links connecting pair of ROIs remained significant ( $p < 0.01$ ). Such significant links were located between pairs of interhemispheric prefrontal regions, between left prefrontal and medial parietal regions (outlining bilateral posterior cingulate cortex, PCC), and between intrahemispheric occipital and temporal regions. Figure 1 shows the



**FIGURE 1** Representation of the significant results of the FC analysis. The red links show a higher connectivity between the pairs of connected regions for the fBD group. All results were corrected by FDR at 0.1

cortical distribution of significant links. PCA analysis revealed two main components, explaining 54% (PLV-pca1) and 12.6% (PLV-pca2) of the information, respectively. In alpha and beta bands, we found differences in FC links, but they did not survive FDR correction at 10%, being not reported as significant. However, these links only become significant after an FDR correction at 15%. Alpha and beta band results are shown in the section “Alpha and beta band FC results” in the supporting information document.

### 3.2 | ANCOVA for neuropsychological scales and FC components

First of all, we calculated a principal dysexecutive component from dysexecutive scales, obtaining a principal component (EXE-pca1) with the 90% of the information regarding dysexecutive behaviours, which we used in the subsequent analyses.

ANCOVA results showed significant differences between fBD and fLD groups for BIS-11 ( $p = 0.049$ ), SSS-V ( $p = 0.002$ ) and EXE-PCA1 ( $p = 0.019$ ), as well as PLV-pca1 ( $p < 0.001$ ). We did not find significant differences for PLV-pca2 ( $p = 0.394$ ). These results point to a higher level of impulsivity, sensation seeking and dysexecutive behaviours prior to alcohol BD onset. Only the covariate of sex exhibited significant differences in SSS-V scale ( $p = 0.011$ ). Table 1 shows the results and statistical parameters of this analysis.

### 3.3 | Correlations with alcohol consumption

The results of correlation analysis showed significant and positive relationships with the consumption ratio for SSS-V ( $p = 0.001$ ), BIS 11 ( $p = 0.016$ ), EXE-pca1 ( $p = 0.016$ ) and PLV-pca1 ( $p = 0.001$ ). We also found significant positive associations between neuropsychological and FC variables, as well as a significant positive correlation between sensation-seeking scores (SSS-V) and sex (see Table 2). Figure S1 in the “supporting information” shows the connectivity links that has significant correlations with neuropsychological traits.

### 3.4 | Multivariate regression model

Those variables that had a significant association with future alcohol consumption (i.e. SSS-V, BIS-11, EXE-pca1 and PLV-pca1) were introduced in a multivariate stepwise regression model. Results revealed a significant model including SSS-V and BIS-11 variables, which explained the 32% of the variance ( $R^2 = 0.32$ ). The EXE-pca1 and PLV-pca1 variables were not significant predicting alcohol consumption scores in this model. Due to the high correlation between SSS-V and FC PLV-pca1, as exploratory analyses, we tested a regression analysis removing SSS-V from the model. This analysis revealed that when sensation seeking is removed, both variables (EXE-pca1 and PLV-pca1, but not BIS-11) were predictors of future alcohol consumption ( $R^2 = 0.31$ ). Table 3 and Figure 2 show the statistical parameters and graphical distribution of these regression models. In order to further explore the relationship between sensation seeking, FC and dysexecutive components, we conducted an exploratory mediation analysis. We hypothesised that FC and dysexecutive traits would be predictive of alcohol consumption throughout its association with sensation-seeking traits.

**TABLE 2** Correlation analysis results

Variables	1	2	3	4	5
1. BD ratio	1				
2. BIS-11	0.342*	1			
3. SSS-V	0.506**	0.244	1		
4. EXE-pca	0.346*	0.510**	0.322*	1	
5. PLV-pca1	0.499**	0.320*	0.417**	0.303*	1

Note: Results of Spearman's correlation with alcohol consumption. BD ratio, number of standard alcohol units drank per session; BIS-11, Barrat impulsivity scale; SSS-V, Sensation-seeking scale form V; EXE-pca, principal component of dysexecutive behaviours (BDEFS, BRIEF and DEX scales); PLV-pca1, principal component (54%) of connectivity differences. \* $p < 0.05$ ; \*\* $p < 0.01$ .

**TABLE 1** ANCOVA results

Variables	fLD $n = 17$ M (SD)	fBD $n = 22$ M (SD)	$F$	$p$	$\eta^2$
BIS-11	46.70 (10.28)	54.68 (13.01)	4.14	0.049*	0.103
SSS-V	3.88 (2.14)	5.77 (1.54)	10.81	<0.01**	0.231
EXE-pca	2.88 (4.10)	5.86 (5.04)	6.06	0.019*	0.144
PLV-pca1	-0.09 (0.06)	0.07 (0.16)	16.50	<0.01**	0.314
PLV-pca2	-0.01 (0.03)	0.01 (0.09)	0.74	0.394	0.020

Note: Results of ANCOVA comparison between groups. BIS-11, Barrat impulsivity scale; SSS-V, Sensation-seeking scale form V; EXE-pca, principal component of dysexecutive behaviours (BDEFS, BRIEF and DEX scales); PLV-pca1, principal component (54%) of connectivity differences; PLV-pca2, second component (12.6%) of connectivity differences. Sex and age were controlled as covariates.

Sex showed a significant effect with SSS-V scale ( $p = 0.011$ ). Corrected for multiple comparisons with Bonferroni method.

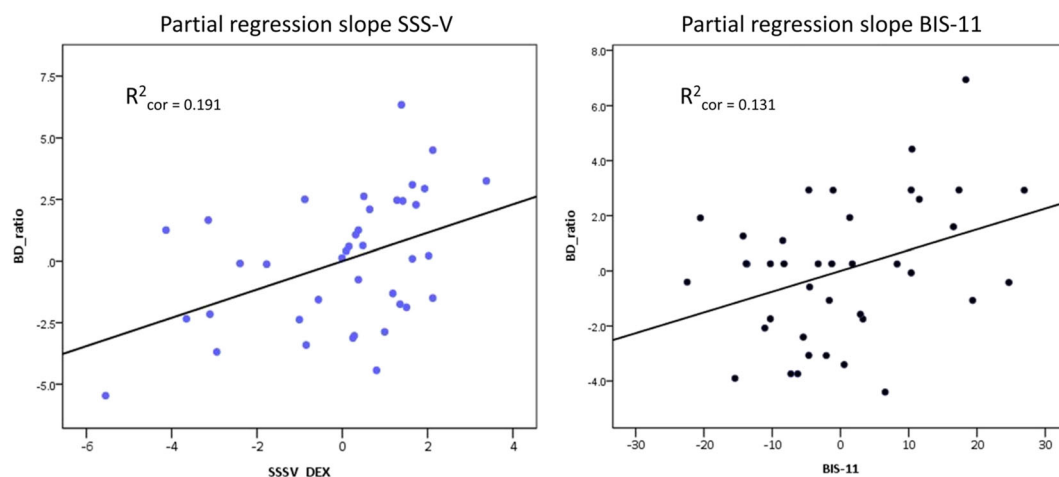
\* $p < 0.05$ ; \*\* $p < 0.01$ .

**TABLE 3** Multivariate stepwise regression model results

Variables	B	E.T (B)	$\beta$	t	p	$R^2_{cor}$
Constant	-2.99	1.79		-1.66	0.104	0.32
BIS-11	0.075	0.032	0.325	2.32	0.026*	
SSS-V	0.575	0.197	0.407	2.91	0.006**	
EXE-pca			0.167	0.976	0.336	
PLV-pca1			0.226	1.43	0.161	
<b>Post-hoc model</b>						
Constant	3.70	0.393		9.43	0.000	0.31
BIS-11			0.144	0.849	0.402	
EXE-pca	0.033	0.014	0.330	2.29	0.028*	
PLV-pca1	6.77	2.63	0.369	2.56	0.015*	

Note: Results of multivariate step-wise regression model. *Dependent variable*, number of standard alcohol units drank per session (BD ratio); BIS-11, Barrat impulsivity scale; SSS-V, Sensation-seeking scale form V; EXE-pca, principal component of dysexecutive behaviours (BDEFS, BRIEF and DEX scales); PLV-pca1, principal component (54%) of connectivity differences.

\* $p < 0.05$ ; \*\* $p < 0.01$ .



**FIGURE 2** Slopes of partial regression for significant predictors of future BD intensity. Left panel shows the dispersion graph and the slope of disinhibited sensation seeking (SSS-V),  $R^2 = 0.191$ . Right panel shows the dispersion graph and the slope of impulsivity (BIS-11),  $R^2 = 0.131$ . Total regression model was significant, with a  $R^2 = 0.323$

### 3.5 | Exploratory mediation analysis

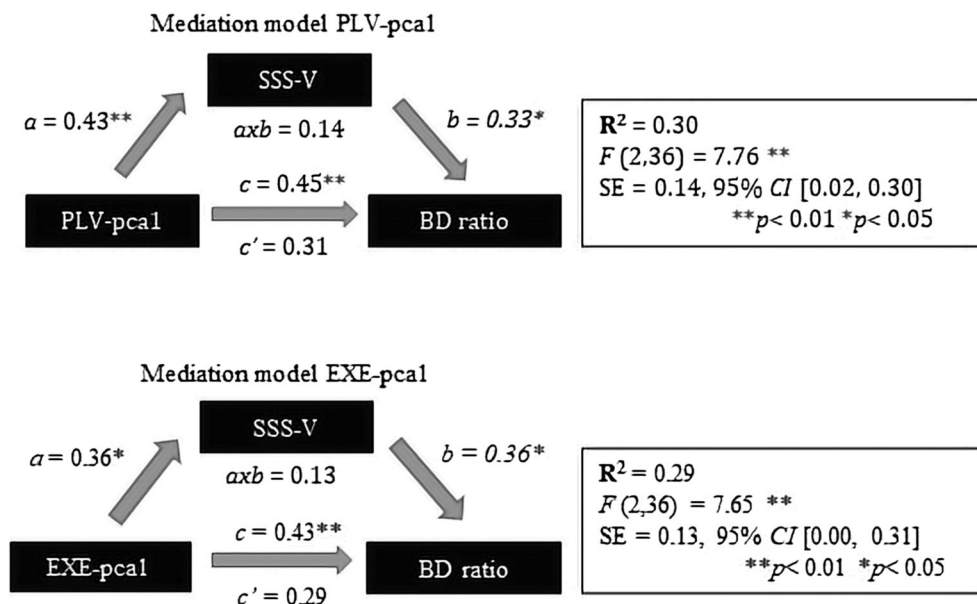
Two different mediation models were conducted to further understand the association between sensation-seeking traits, dysexecutive behaviours and electrophysiological connectivity in relation to the development of BD habits. For both models, sensation-seeking traits (SSS-V scores) were used as the mediating mechanism and the alcohol consumption ratio (SAUs) as the dependent variable. For the first model, PLV-pca1 was used as the independent variable. The results showed that there was complete mediation, explaining 30% of the

variance, in which FC has an effect on future alcohol consumption (SAUs) through the mediation mechanism disinhibited sensation seeking (SSS-V) ( $ab = 0.14$ ;  $CI = [0.019; 0.309]$ ).

In the second model, we introduced EXE-pca1 as the independent variable. The overall model was significant, explaining 29% of variance. However, in this model the direct effect of dysexecutive behaviours (EXE-pca1) on alcohol consumption ratio and the indirect effect through the mediation mechanism (sensation seeking) did not survive after bootstrapping correction. Figure 3 shows the representation and statistical parameters of both models.



**FIGURE 3** Results of exploratory mediation models. Upper panel shows mediation model using disinhibited sensation seeking (M; SSS-V) as mediator between dysexecutive component (X; EXE-pca1) and future BD intensity (Y; BD ratio). Lower panel shows mediation model using disinhibited sensation seeking (M; SSS-V) as mediator between functional connectivity component (X; EXE-pca1) and future BD intensity (Y; BD ratio)



## 4 | DISCUSSION

This study aimed to characterise neuropsychological traits and electrophysiological connectivity profiles as potential predictors of the risk of developing alcohol BD behaviours during adolescence. Our main results highlighted those adolescents who engaged in BD 2 years later showed, prior to BD onset, abnormal resting-state gamma-band hyperconnectivity. In addition, they exhibited increased traits of impulsivity, sensation seeking and dis-executive behaviours. Furthermore, we underline the importance of impulsivity and sensation-seeking traits as main predictors of BD, as well as the role of the latter, as a mediator of the relationship of BD with dysexecutive and basal hyperconnectivity.

Several works have pointed out the association between impulsivity, sensation seeking, and low executive regulation with the development of AUD and BD.<sup>11,42</sup> Also, such a relationship has been confirmed experimentally in previous studies.<sup>10,26,43</sup> The development of these neuropsychological traits has been described as the consequence of neglected development of cognitive, emotional or behavioural self-regulation (SR) abilities.<sup>44,45</sup> SR skills rely on executive control processes as cognitive and IC capacities,<sup>45,46</sup> which develop through the lifespan, but particularly during adolescence.<sup>27,47</sup> This new social and motivational context opens the door to the exploration of new experiences and forms of leisure, leading in most cases to substances of abuse. According to dual systems maturation theories,<sup>12</sup> such motivational transition comes together with profound maturational changes in subcortical reward systems, followed by the high-order control networks. In sum, the different dimensions that build SR skills depend, in turn, on the optimal functioning of such cortical systems,<sup>48</sup> and the balance between reward-driven behaviours and self-control abilities.<sup>45</sup>

Sensation seeking has been demonstrated to play an important role in risky and rewarding behaviours.<sup>49</sup> However, sensation seeking

itself cannot be considered an isolated factor for maladaptive behaviours such BD.<sup>31</sup> This psychological trait is the motivational drive that exposes the individual to risky situations, where prefrontal executive systems must exert their control to suppress inadequate behaviour and negative outcomes. In this regard, our results are in line with previous studies that have pointed out the mediating relationship of sensation seeking with neurocognitive abilities in the outcome of maladaptive and drinking behaviours.<sup>50,51</sup> Furthermore, we found that sensation seeking is an important mediating mechanism in electrophysiological dynamics and appears to be a crucial factor in the development of future BD through its relationship with abnormal hyperconnectivity prior to alcohol consumption. Thus, abnormal functional dynamics in conjunction with dysfunctional executive control seem to modulate the consequent risk of developing hazardous habits such as BD among adolescents.

Our findings on the FC profiles highlight the presence of a gamma-band hypersynchronisation for the fBD group, localised between the prefrontal, medial fronto-parietal and occipito-temporal interhemispheric networks. This functional distribution seems to encompass the main resting-state networks, such as the Default Mode Network (DMN), the Salience Network (SN) and the Executive Core Network (ECN).<sup>52</sup> Within these networks, we find core differences in the medial parietal regions (particularly in the PCC),<sup>53</sup> as well as medial (including the anterior cingulate cortex, ACC) and orbital PFC.<sup>54</sup> Functional alterations in DMN have been widely associated with several psychiatric and neurological disorders, as well as with BD and AUD.<sup>6,55</sup> Moreover, abnormalities in its functional dynamics may be related to several difficulties in the performance of executive control processes.<sup>56,57</sup> Similarly, SN and ECN abnormalities, which underlie the development of high-order cognitive capacities,<sup>52,58</sup> have also appeared altered in BD and AUD<sup>59,60</sup> and other psychiatric conditions with dysfunctional behavioural regulation (i.e. attention deficit hyperactivity disorder). However, resting-state FC abnormalities, before

alcohol BD, have been scarcely studied. To our knowledge, only one work performed using fMRI explored global FC profiles in this population, reporting similar patterns of functional hyperconnectivity, and increased impulsivity.<sup>24</sup> However, to date, electrophysiological evidence remained unexplored. While few studies have investigated basal electrophysiological FC for BD and AUD, overall, our findings appear to be in line with the hypersynchronisation characteristic of these populations.<sup>6,23</sup> Furthermore, the present results seem to indicate, for the first time, that such deviations in resting-state FC may exist before the onset of alcohol abuse. Thus, early abnormalities in these core functional networks may be associated with dysfunctions in SR skills and, consequently, with behavioural dysregulations during adolescence. This interpretation seems to be supported by the positive correlations between FC and neuropsychological traits and, in particular, by the mediating role of sensation seeking in the association between abnormal FC and future alcohol abuse.

The origin and function of local and large-scale gamma oscillations have been related to various cognitive processes and sensory integration.<sup>61</sup> Its neurobiological origin is commonly located in the interleaved activity of inhibitory interneurons complexes (INI) and pyramidal neurons.<sup>62</sup> Its fundamental role is to stabilise the cortical excitation/inhibition balance through GABAergic inhibition of pyramidal neurons. This function is regulated mainly by dopaminergic afferents (through DRD1 and DRD2 receptors), and glutamatergic afferents on a lesser scale (through NMDA receptors).<sup>63</sup> Interestingly, the regulation of cortical excitability exerted by INI complexes does not become fully optimised until early adulthood (Tseng & O'Donnell, 2007<sup>64</sup>). Therefore, dysfunction of this GABAergic mechanism may lead to an aberrant increase in cortical excitability,<sup>65</sup> manifested as alterations in functional synchronisation and spurious hyperconnectivity, predominantly in fast frequency bands, such as beta and gamma.<sup>66,67</sup> Furthermore, some interesting computational work has shown how the correct function of INIs is necessary to maintain the stability of functional networks, with patterns of aberrant hyperconnectivity appearing after different types of dysfunction.<sup>68</sup>

Within this framework, the hyperconnectivity profiles found in this study could rest on abnormalities of these inhibitory mechanisms. In this line, GABAergic dysfunction is associated with alterations in functional synchronisation, both in animal<sup>69</sup> and human models.<sup>70</sup> In an extensive review, Duncan and colleagues (2014) reported how, in general terms, GABAergic levels in different brain regions showed a negative relationship with functional synchronisation in several resting-state networks. Specifically, some studies have found a negative correlation between functional synchronisation in the DMN and GABA levels in the PCC<sup>71–74</sup> and mPFC.<sup>75</sup> These studies seem to support the idea of potential abnormalities in GABAergic inhibition mechanisms underlying the hyperconnectivity found in the fBD group. In the same framework of current research, a previous work similarly reported increases in beta-band FC during the execution of IC tasks, particularly among important DMN, SN, and ECN nodes (such as ACC, mPFC, hippocampus and lateral PFC).<sup>26</sup> Current evidence suggests that such electrophysiological phenotypes may not be dependent on

the current cognitive state but are likely related to a deeper neurobiological hyper-excitability.

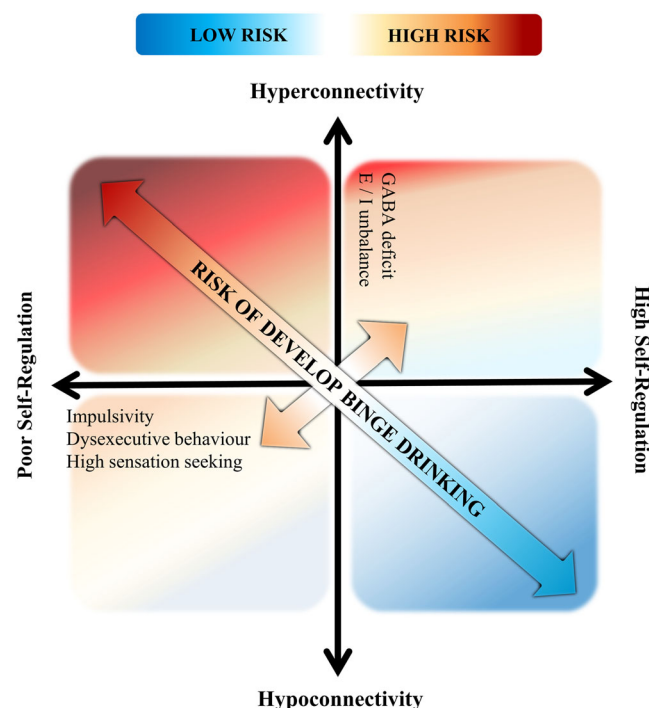
Regarding neuropsychological traits, there is additional evidence associating dysfunctions in GABAergic neurotransmission with such cognitive phenotypes, providing a common framework for understanding electrophysiological and cognitive abnormalities. In an extensive review on animal and human models, Hayes and collaborators (2014)<sup>76</sup> depicted the association between lower GABAergic levels in various brain structures (notably the mPFC and ACC), higher impulsivity and poorer executive control. Subsequent works in animal and human models show how decreased GABA synthesis in the PFC<sup>77</sup> or impairments in the function of GABA<sub>A</sub> receptor<sup>78</sup> represent a marker of impaired executive control and impulsivity.<sup>79,80</sup> Interestingly, increased brain excitability has been associated with higher sensation-seeking phenotypes and subsequent substance abuse,<sup>81</sup> highlighting the positive relationship with FC found in current work.

Based on the above, these neurobiological differences could underlie the phenotypes of electrophysiological hyperconnectivity and dysfunctional neuropsychological traits as vulnerability factors for the development of risk behaviours. Figure 4 provides a schematic theoretical model of the risk of developing BD as a function of FC and SR capacities.

Finally, some limitations must be considered. Although the sample size was large enough to detect differences with high effect sizes, larger and independent samples should be used to confirm current evidence. Additionally, SR traits should be supported with objective neuropsychological assessments of executive performance to improve the characterisation of neurocognitive domains and their relationship with electrophysiological profiles. Other psychological traits such as social anxiety and depression should be considered in future studies, since they are an important factor in alcohol consumption, and maybe present even before BD onset.

In conclusion, the evidence provided during this work seems to confirm the existence of differences in SR traits and resting-state electrophysiological networks before alcohol consumption. This evidence should provide an important step forward in the identification of those adolescents at risk of developing risky behaviours such as BD. However, the neurobiological and psychological nature of these abnormalities in early adolescence remains unclear. Further research should answer the questions raised by this work by exploring in-depth the neuromaturational substrate underlying the risk phenotypes. Moreover, potential clinical implications arise from this new evidence. Thanks to the identification of the most vulnerable neuropsychological traits of at-risk adolescents, the door is open to developing cognitive training programmes to strengthen and provide tools against the development of maladaptive behaviours. Likewise, the identification of the neurofunctional correlates of such behaviours allows for new perspectives of intervention, such as neuromodulation. The benefits of these tools in the modification of neurocognitive abilities are being tested,<sup>82</sup> being a promising path for intervention on BD behaviours.<sup>83</sup> This growing knowledge should support the development of better prevention and intervention programmes, geared to meet the needs and motivations of the unique adolescent brain.





**FIGURE 4** Theoretical model of risk of develop BD. Axis represents the level of electrophysiological functional connectivity (Y) and self-regulation skills (X). Color legends show a gradient of risk to develop BD habits, from deep blue (very low risk) to deep red (very high risk). Lower risk scenario is characterised by low or “normal” levels of FC and high SR capacities (right-inferior quadrant). Higher risk is defined as higher levels of FC and poor SR skills (left-superior quadrant). Having excessive FC levels are proposed as a crucial factor of vulnerability on top of SR skills (right-superior quadrant). Such risk phenotypes are identified with psychological traits of impulsivity, dysexecutive behaviours and high sensation seeking. FC hyperconnectivity is proposed as consequence of different neurobiological backgrounds, such GABAergic deficits and excitation/inhibition unbalances

## CONFLICT OF INTEREST

There is no conflict of interest for any of the authors.

## AUTHORS CONTRIBUTION

All authors of the present work have made substantial contributions to its elaboration. LM G-M and F M designed this research line and outlined the main experimental stages. LF A-T, LM G-M, C P, P M-G and R G recruited the participants for this study and collected data and questionnaire evaluations. LF A-T, R B, D S and A D-L performed MEG data preprocessing and analyses, while LF A-T, D S, A D-L, C P, P M-G, R G and LMG-M analyzed data from questionnaires. All authors contributed to the redaction and supervision of this manuscript. F M and LM G-M approved the final version of this work.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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