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Abnormal organization of inhibitory control functional networks in future binge drinkers

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ABSTRACT

Background and aims: Adolescent Binge drinking has become an increasing health and social concern, which cause several detrimental consequences for brain integrity. However, research on neurophysiological traits of vulnerability for binge drinking predisposition is limited at this time. In this work, we conducted a two-year longitudinal study with magnetoencephalography (MEG) over a cohort of initially alcohol-naive adolescents with the purpose of characterize inhibitory cortical networks' anomalies prior to alcohol consumption onset in those youths who will transit into binge drinkers years later.

Methods: Sixty-seven participant's inhibitory functional networks, and dysexecutive/impulsivity traits were measured by means of inhibitory task (go/no-go) and questionnaires battery. After a follow-up period of two years, we evaluated their alcohol consumption habits, sub-dividing them in two groups according to their alcohol intake patterns: future binge drinkers (fBD): n = 22; future Light/non-drinkers (fLD): n = 17. We evaluated whole-brain and seed-based functional connectivity profiles, as well as its correlation with impulsive and dysexecutive behaviours, searching for early abnormalities before consumption onset.

Results: For the first time, abnormalities in MEG functional networks and higher dysexecutive and impulsivity profiles were detected in alcohol-naïve adolescents who two years later became binge drinkers. Concretely, fBD exhibit a distinctive pattern of beta band hyperconnectivity among crucial regions of inhibitory control networks, positively correlated with behavioral traits and future alcohol intake rate.

Conclusions: These findings strongly support the idea of early neurobiological vulnerabilities for substances consumption initiation, with inhibitory functional networks' abnormalities as a relevant neurophysiological marker of subjects at risk— we hypothesize this profile is due to neurodevelopmental and neurobiological differences involving cognitive control networks and neurotransmission pathways.

1. Introduction

Binge Drinking (BD) is the most prevalent alcohol misuse during adolescence. Its prevalence and damage make it a significant public health concern. (Courtney and Polich, 2009a). BD is characterized by the intake of at least four standard drinks for women and five for men within two hours, followed by days of abstinence (Courtney and Polich, 2009a). The BD intake usually causes intoxication, defined as a blood alcohol concentration (BAC) at or above 0.08 % (Courtney and Polich, 2009a).

Adolescents are in a critical neurodevelopmental period which involves prominent neurobiological changes, engaging particularly high-order association brain regions, making them especially vulnerable to the adverse health outcomes of BD (Blakemore and Choudhury, 2006).

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Several studies assessing adolescents binge drinkers have pointed out that the brain maturational course could potentially be altered by the effects of ethanol neurotoxicity, causing neuroanatomical (Bava and Tapert, 2010) and neurophysiological impairments (Correas et al., 2016, 2019; López-Caneda et al., 2017). However, it is important to note that the cross-sectional nature of these type of studies on binge drinkers makes it impossible to infer a conclusion about whether the neurocognitive impairment of BDs is just due to alcohol consumption or if there exist prior abnormal brain networks driven such behaviours.

Some authors have proposed the presence of abnormal neurocognitive and neurological developments, mainly associated with inhibitory control (IC) processes, as a vulnerability factor that increases the probability of engaging in BD or any risk-taking behaviour (López-Caneda et al., 2014c; Verdejo-García et al., 2008). Accordingly, some works have detailed early differences both in brain's structural (Brumback et al., 2016; Pehlivanova et al., 2018) and functional (Squeglia et al., 2017) integrity related with future alcohol consumption. However, in our knowledge, neurophysiological signatures of this complex behaviour have not been addressed and cannot be just the consequence of the disruption of particular areas. It will probably be associated with an abnormal development of the executive control networks involving the interaction of multiple brain regions.

Brain Functional Networks (FN) can be described by evaluating the oscillatory activity in the time-frequency domain using magnetoencephalography (MEG) (Brookes et al., 2011). The study of the functional connectivity (FC) — defined as the existence of statistical dependencies between the activities of two or more brain sites (Friston, 1994)— may reveal important information regarding FN integrity and efficiency (Rubinov and Sporns, 2010), regarding several neuropsychiatric conditions as well as neurocognitive dysfunction (Baillet, 2017; López-Sanz et al., 2017). MEG FC has been commonly estimated under the hypothesis of phase synchronization (Varela et al., 2001). Among different analytic approaches, phase locking value (PLV) is a widely employed metric, due to its highest test re-test reliability and robustness (Garcés et al., 2016a)

The current longitudinal study aims to characterize potential neurophysiological abnormalities in the functioning of inhibitory control networks as well as related dysexecutive and impulsivity profiles of adolescents who will transit into BD years later. For this purpose, we carried out a two-year longitudinal study with MEG across a sample of alcohol-naïve adolescents. We analysed FC networks during a classical inhibitory task (go/no-go), and high-ecological questionnaires to assess dysexecutive and impulsivity profiles in order to depict FN anomalies before BD initiation. To our knowledge, this is the first study assessing the hypothesis of an abnormal neurophysiological organization of inhibitory control networks regarding this matter. Therefore, our aim is to enhance the evidence of early neurobiological vulnerabilities associated with the onset of BD and other risky behaviours.

2. Methods and materials

2.1. Participants

611 young adolescents (mean age = 14.5 ± 0.9), reporting no previous alcohol intake episodes or related family antecedents, and no psychiatric or neurological disorders, were recruited from different secondary schools of the Community of Madrid (Spain). Initially, participants from the complete sample fulfilled an impulsivity/dysexecutive behaviour questionnaire battery to assess executive behaviour and personality traits. A representative subsample of the participants (n = 67; all right-handed), randomly selected from those performing the neuropsychological tests, underwent a neuroimaging study (MEG and MRI). Two years later, a total of 53 participants completed second evaluation's protocol. In this stage, their alcohol consumption habits were assessed with a semi-structured personal interview and the AUDIT questionnaire (Alcohol Use Disorders Identification Test) (Courtney and Polich, 2009b). During semi-structured interview we inquired individual for any consumption episode in the 2 years follow-up period. If positive, we asked them to describe as accurate as possible a "typical intake episode" in the last 6 months (type of beverage, quantity and time intervals), as well as number of episodes in the last year, and temporal separation between them. Taking account of this information, participants were divided into two groups: one of future binge-drinkers (fBD), and one of those who remained as no-drinkers or transitioned into future light drinkers (fLD). The main criterion for BD classification was to reach a four (females) or five (males) standard drink threshold in a typical drinking episode. Contrary, individuals with a consumption rate at or below two standard drinks per episode were classified as light/no drinkers. In order to have two groups clearly differentiated in alcohol consumption, we ruled out six participants with an intermediate alcohol intake rate. Six participants were also discarded due a deficient completion of AUDIT questionnaire or semi-structured interview, with poorly detailed consumption habits. Similarly, individuals showing a task inhibition accuracy below 70 % were also omitted (n = 2). The final sample was composed of 22 fBD (age 14.6 ± 0.8; eight females) and 17 fLD (age 14.5 ± 0.8; eight females). All participants and their parents or legal guardians signed an informed consent for each stage of the study, following the guidelines in the declaration of Helsinki. The ethical committee of the Complutense University of Madrid approved the study.

2.2. MEG acquisition

MEG data was 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 using an offline signal space separation method (Taulu and Simola, 2006), and subject movements were compensated using the same algorithm. The acquired data was segmented in event related epochs, and artifacted epochs were discarded from subsequent analyses. The procedure is extensively detailed in the "supplementary materials and methods".

2.3. MRI acquisition

A structural MRI was obtained from each participant using a General Electric Optima MR450w 1.5 T machine. Imaging protocol consisted in 3D T1-weighted high-resolution images with the following parameters: TE = 4.2, TR = 11,2 and TI =450 ms, Flip angle = 12°, FoV = 100, acquisition matrix = 256 × 256, and slice thickness =1 mm.

2.4. Inhibitory Task: go/no-go

An equiprobable go/no-go task measured the performance of inhibitory networks in the subjects (Correas et al., 2019; Lavric et al., 2004; López-Caneda et al., 2014a). Fig. 1 shows structure and time intervals for each trial presentation.

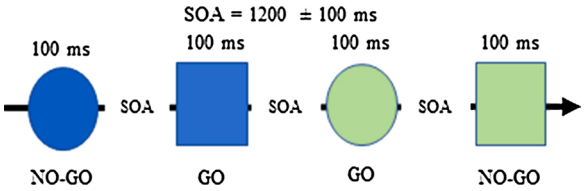

Fig. 1. "Task Go/No-Go Trial Structure". Representation of task go/no-go trial procedure. Stimulus were presented for 100 ms. Participants had the instructions to press a bottom as fast as possible each time they see a "GO" target appears. SOA = stimulus onset asynchrony.

2.5. Executive function and impulsivity assessment questionnaires

We selected four widely used scales to assess the level of executive performance and impulsivity in an ecological way: Barkley Deficits in Executive Function Scale (BDEFS); Barratt Impulsivity Scale (BIS-11); Dysexecutive Questionnaire (DEX), and Sensation Seeking Scale (SSS-V). Further details are included in "supplementary materials and methods" section.

2.6. Data analysis

MEG data was transformed to source space using a realistic single shell (Nolte, 2003) as forward model and a Linearly Constrain, Minimum Variance (LCMV) beamformer (Van Veen et al., 1997) as inverse model. Using individual T1 images, data was reconstructed independently into source space for the classical bands: theta (4–8 Hz), alpha (8–12 Hz), low beta (12–20 Hz), high beta (20–30 Hz) and low gamma (30–45 Hz) Quality assessment of the reconstructed source signals were calculated by the reconstruction of the early visual component around 100 ms. These assessments are depicted in Supplementary Fig. S1. The source model consisted on 1188 cortical sources, labelled according to the Automatic Anatomical Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002). FC was estimated under the hypothesis of phase synchronization by means of the Phase Locking Value (PLV) (Bruña et al., 2018) in four different time windows: 150–450 ms, 150–250 ms, 250–350 ms and 350–450 ms. In order to study the inhibition mechanisms in the brain while reducing the influence of artefacts, only the correct inhibition trials were analysed. In a first step, PLV was calculated separately for each pair of source positions, generating a 1188 by 1188 FC matrix per time window (Fig. 2, part 1). From this whole-brain FC matrix we took three approaches, depicted in different parts of Fig. 2. In the first approach we averaged the PLV values of all the links connecting each pair of cortical areas of the AAL atlas (Fig. 2, part 2), generating a 76 by 76 whole-brain FC matrix (Fig. 2, part 4). In the second approach, we calculated the nodal strength (the sum of the PLV values of all the links arriving to a source for each position (Fig. 2, part 5), resulting a 1 by 1188 vector of nodal strengths. In the third approach we averaged the PLV values of a set of regions-of-interest with every cortical source (Fig. 2, part 6), generating a set of 1 by 1188 seed-based FC vectors per seed (Fig. 2, part 7). Additionally, we performed several quality-check analyses in order to enhance the robustness of our results and minimize or remove potential artefact-driven outcomes. This procedure is extensively detailed in the "supplementary materials and methods".

2.7. Statistical analysis

The questionnaires' scores were compared between groups using a 1-way ANOVA. Source-level FC statistical analyses were performed separately for whole-brain (area-based) connectivity, nodal strength, and seed-based connectivity.

For the whole brain analysis, the PLV value between each pair of areas was compared between groups using an ANCOVA test using age as covariate and sex as factor. The resulting *p*-values were corrected for multiple comparisons with a False Discovery Rate (FDR) of 0.10 (Benjamini and Hochberg, 1997). The resulting FDR-corrected alpha threshold was 0.0014, and only *p*-values below that threshold were reported as significant (Fig. 1A). To help the interpretation of the results, we calculated the correlation between the FC at these significant links and the questionnaires' scores, correcting the results by multiple comparisons using an FDR of 0.10.

For the nodal strength analysis, the data consisted of a single value per source. These values were compared between groups using a cluster-based permutation test (CBPT) (Oostenveld et al., 2011). The nodal strength values were compared between groups using an ANCOVA contrast with age as covariate and sex as factor. The *p*-values were corrected by multiple comparisons (the number of clusters) using a stepwise Bonferroni approach. Only clusters surviving this correction are reported as significant (Fig. 1B).

For the seed-based analysis, the statistical approach was identical to that for the nodal strength. Three relevant seeds were selected from the previous literature in cognitive control, alcohol-related pathology, and premorbid findings: ACC (24 source positions), rIFG (44 source positions) and lHip (13 source positions). Last, a fourth seed was included in this analysis: the region defined by the cluster showing significant differences between both groups in the nodal strength analysis (Fig. 1C).

3. Results

3.1. Questionnaires battery

A total of 611 alcohol-naive participants were evaluated using a set of self-informed questionnaires and split, after a two-year follow up, into fBD and fLD. In this whole sample, both groups showed differences for every scale evaluated (BDEFS: $p = 0.010$; DEX: $p < 0.001$; BIS-11: $p < 0.001$; SSS-V: $p < 0.001$). When using only the MEG subsample ($n = 39$), results exhibited significant values for SSS-V ($p = 0.0031$), BIS-11 ($p = 0.0332$), DEX ($p = 0.0262$) and a tendency towards significance for BDEFS ($p = 0.0551$). These results point to a higher level of disinhibition, impulsiveness and dysexecutive symptomatology among fBD group, compared with fLDs.

3.2. Inhibitory task go/no-go performance

Sixty-seven participants underwent go/no-go task while MEG cortical activity was recorded. Behavioural performance of final sample composed by 39 subjects (22 fBD and 17 fLD) were analysed. Participant's performance did not differ between groups in response accuracy (fBD 89,67 % ± 9,00 %, fLD 91,61 % ± 6,86 %, $p = 0.48$), inhibition accuracy (fBD = 85,96 % ± 9,31 %, fLD = 86,68 % ± 9,28 %, $p = 0.81$) or response time (fBD = 526,75 ± 53,71 ms, fLD = 507,81 ± 63,84 ms, $p = 0.32$). Indicators of each subject performance for both groups are displayed in Table S1.

3.3. Whole brain network

The first analysis consisted on an atlas-based whole-brain analysis, where we compared the FC patters of both groups during the execution of the task. The FC connectivity patterns did not show any significant difference between the groups for the time windows of 150−250 ms, 350−450 ms nor the complete time window of interest 150−450 ms. Regarding the time window between 250 and 350 ms after the stimulus, low beta band revealed a network comprised of 40 links after FDR correction (significance threshold 0.0044). All 40 links showed hyperconnectivity in the fBD group when compared to the fLD group. Fig. 3A shows the detailed distribution of these links, connecting prefrontal, temporal and motor regions. Table 1 shows the mean PLV values for each significant link. All significant links were corrected for source leakage bias. Complementarily, we performed a correlation analysis between significant links and alcohol intake rates of all participants, including those with an intermediate alcohol intake. As general trend, we found significant positive correlations in almost all of 40 links with rho values between 0.32 and 0.53. Figure S8A shows scatter plots of the correlation for each of the 40 significant links.

3.4. Correction of source leakage bias

Phase synchronization metrics such PLV are known to suffer from source leakage effects, whereby reconstructed activity of a source leaks to a nearby source location. This effect spuriously increases instantaneous FC values (zero-lag synchronization), confounding the origin of results. We addressed this problem in two different approaches: Zero-lag-insensitive metric (ciPLV) and direct estimation of source leakage

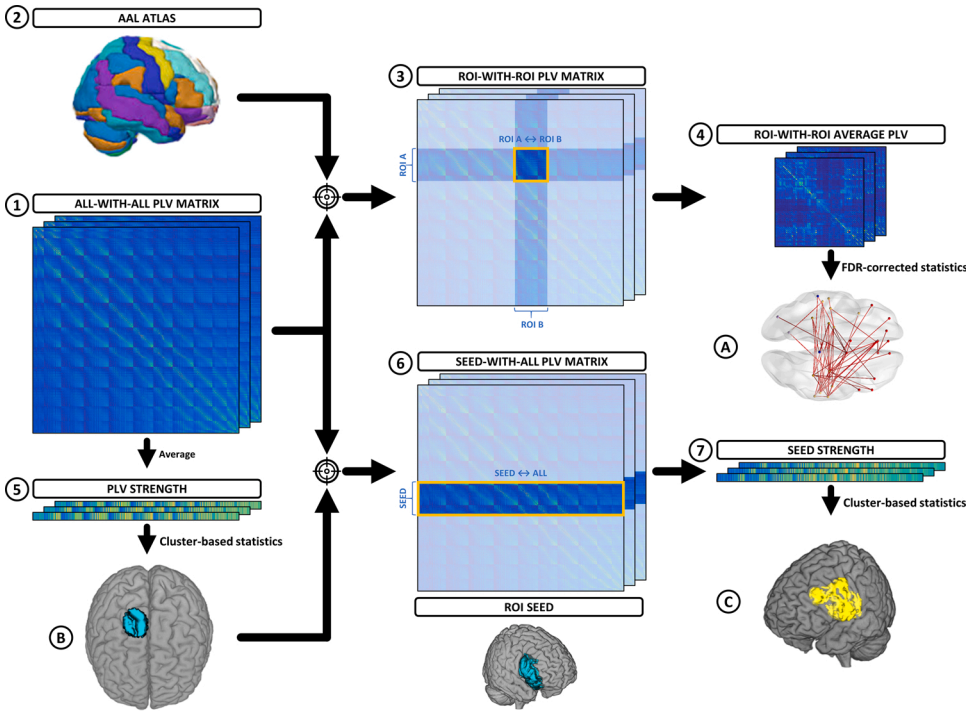

Fig. 2. "PLV Methods Summary". Different FC calculation methods: **Whole-brain inter-ROI (A), Strength (B) and Seed-based (C)**. The global connectivity matrix **(1)** represents FC values of between each pair of cortical source positions (1188 × 1188). The values in **(1)** were averaged taking all the pairs of sources connecting each pair of ROIs **(3)** in the Automated Anatomical Labeling atlas **(2)**, obtaining a (76 × 76) matrix of inter-area FC **(4)**. The connectivity values in **(4)** were compared between groups and corrected using a False Discovery Rate to obtain statistically significant hypo- or hyper-connected pairs of ROIs **(A)**. The strength values in **(5)** were calculated by summation of all the PLV values connecting to each source position in **(1)**. The values in **(5)** were compared between groups using a Cluster-Based Permutation Test to obtain statistically significant regions of global hypo- or hyper-connectivity **(B)**. Finally, values of connectivity in **(1)** for the source positions obtained in **(B)** were selected **(6)** and averaged to obtain a global value of connectivity from the seed obtained in **(B)** and the rest of the brain **(7)**. The values in **(7)** were compared between groups using a Cluster-Based Permutation Test to obtain regions of the brain hypo- or hyper-connected with the seed **(C)**. The analysis in **(C)** was also conducted using some especial ROIs from the anatomical atlas **(2)**, namely anterior cingulate, right inferior frontal gyrus and left hippocampus.

(Beamformer filter correlation). "Supplementary material Fig. S5" displays results using ciPLV metric, with more than half of the links (57%), surviving this correction. However, zero-lag-insensitive metrics have showed low test-retest reliability in MEG data (Colclough et al., 2016; Garcés et al., 2016b), and ignores bidirectional and indirect true connections (Gollo et al., 2014; Petkoski et al., 2018). For this reason, we employed a direct estimation of source leakage (beamformer filters correlation) as a covariate in our statistical comparisons. This approach removes successfully the leakage differences between groups, showing that 100% of our significant links seems free of source leakage bias. These procedures are detailed in depth in "Supplementary materials and methods".

3.5. Whole-brain correlations

In order to evaluate the relation between the FC patterns showing differences between both groups and the self-informed questionnaires, we performed a correlation analysis between their scores and the FC values in the 40 significant links described before. We found a positive correlation between several significant links and BIS-11 (two links) and SSS-V (21 links) scores ($p = 0.020$). For DEX, we found positive correlations, but they did not survive FDR correction. BDEFS did not present significant results in correlation analysis. Fig. 3B displays the detailed distribution of links with significant correlations. Figure S7A shows scatter plots for every significantly correlated link.

3.6. Nodal strength & seed based

On a second approach we evaluated the differences in FC between both groups while minimizing the anatomical constrain of the atlas parcellation. We selected three a-priori ROIs (ACC, rIFG, and lHip), and calculated a fourth data driven ROI (termed strength seed). Last, we compared, using a cluster-based permutation test (CBPT), the level of seed-based FC between both groups. Based on the results shown in the previous section, this analysis was focused only in the low beta band. The results for the seed-based analysis are summarized in Table 2.

For the selection of the fourth ROI, we used an atlas free approach to find differences in connectivity not circumscribed to a specific anatomical region. First, we found the continuous cluster showing a higher difference in overall connectivity between both groups. The result is an area where the connectivity with the rest of the brain is different between the groups. However, it is not possible, with this information, to know to which areas this cluster shows increase or decrease in connectivity. To do so, we performed a second-step analysis using this cluster as seed. First, we compared the nodal strength for each source position between both groups, using a cluster-based permutation test (CBPT). The result was a significant cluster ($p = 0.0266$) comprising mainly the right supplementary motor area (rSMA), as depicted in Fig. 4A. The nodal strength of this cluster was higher for the fBD than for the fLD, indicating a global hyperconnectivity in the first group. In addition, Supplementary Fig. S2 shows a depiction of the average nodal strength for each group, where an apparent higher level of nodal strength can be observed in the fBD group.

When using the strength seed, we found three significant clusters ($p < 0{,}0001$; $p = 0.0004$; $p = 0.0176$) showing an increased level of FC with the seed in the fBD when compared to the fLD. The spatial distribution of the three clusters is depicted in Fig. 4B.

When comparing the level of global FC with the ACC between groups, we found three significant clusters ($p = 0.0009$; $p = 0.0195$; $p = 0.0247$) showing a higher level of FC in the fBD group. The spatial distribution of the clusters is shown in Fig. 5A. The first, most significant, cluster comprised right parietal and superior frontal areas. The second cluster comprised right superior temporal areas. Last, the third cluster comprised left frontal areas, mainly motor regions, but did not survive the stepwise Bonferroni correction.

When comparing between groups the level of global FC with the lHip, we found three significant clusters ($p = 0.0096$; $p = 0.0116$; $p = 0.0149$) were the FC in the fBD group was higher than in the fLD group.

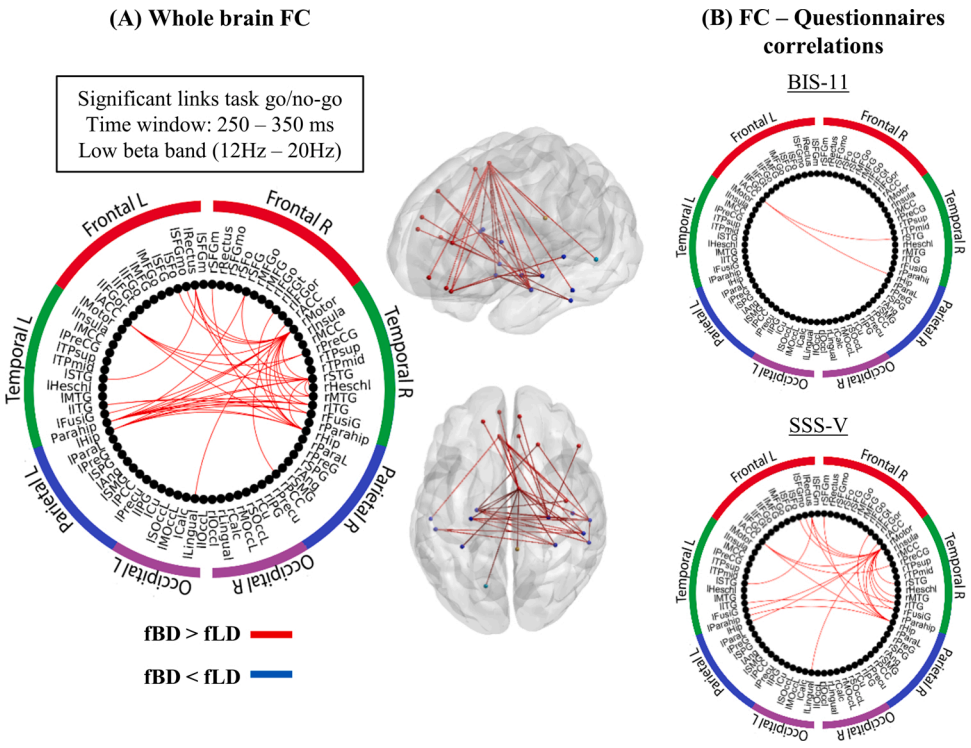

Fig. 3. "Task Whole-Brain Functional Network And Correlations". **(A)** Representation of results of task in the inhibitory condition (no-go) at 250 - 350 ms time window in low beta band. Red links reflect significant inter-ROI hyper-connection (fBD > fLD) under FDR correction at 0.10. All significant links are corrected for source leakage bias by beamforming filter covariation **(B)** *FC - Questionnaires correlations:* Representation of significant correlation between task's **significant** FC links and tests scores. Red links reflect positive correlations between links found in task (no-go condition) and dysexecutive/impulsive tests (BIS-11 and SSS-V). Correlation were corrected by multiple comparison FDR 0.10. The results show that the higher the FC values the higher the impulsivity and sensation seeking traits (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

The spatial distribution of these clusters is depicted in Fig. 5B. The first cluster comprised right superior temporal areas. The second cluster comprised right posterior frontal areas. Last, the third cluster comprised right superior temporal areas.

Last, when comparing the level of FC with the rIFG between groups, we found one significant cluster ($p = 0.0088$) showing a higher level of connectivity between this region and the right posterior temporal lobe in the group of fBD, when compared to the fLD group. The spatial location of this cluster is shown in Fig. 5C. Similarly, we performed a correlation analysis between FC values of significant clusters and alcohol consumption rate. We found significant positive correlations for all tested clusters, with rho values between 0.44 and 0.65.

In order to deepen examine these results, the Supplementary Fig. S3 includes a depiction of the seed-based FC separately for each group. As indicated by the statistical analysis, in all cases the seed-based FC values are higher in the fBD group than in the fLD group.

4. Discussion

The aim of the current study is characterizing the existence of abnormal neurophysiological FN related to future alcohol consumption in a cohort of alcohol-naive adolescents. The main results point to distinctive traits of dysexecutive and impulsive behaviours and abnormal organization of the inhibitory control FN in young people who transitioned two years later into binge drinkers.

The relationship between dysexecutive and impulsive profiles and cognitive control networks has been largely supported by prior studies (Spinella, 2004; Zandbelt and Vink, 2010). Moreover, a recent study associated prefrontal brain development abnormalities along adolescence with impulsivity traits (Ziegler et al., 2019). Furthermore, these particular traits have been demonstrated to be tightly associated with substance consumption and addictive behaviours, and proposed as a crucial factor in the vulnerability towards initiation of drug consumption (López-Caneda et al., 2014c). In this line, our results support previous argues, and these traits as markers of adolescents who are prone to initiate alcohol consumption.

Furthermore, for the first time, we found an abnormal functioning of the brain FN in fBDs by means of a longitudinal study with MEG. One main phenomenon associated with fBD profiles was found: a wide extended hypersynchronization profile. This abnormal pattern of connectivity engage a cortical fronto-temporal distribution (and particularly SMA, ACC, rIFG and lHip) and temporal dynamics (250–350 ms time-window) associated to IC cortical processes (Aron et al., 2014). Disruption of the IC processes, has been prominently associated with behavioural traits such impulsivity and dysexecutive profiles, and consistently altered in AUD (López-Caneda et al., 2013). Some previous studies reported patterns of hypersynchronization on BD population as potential adverse consequences of continuous BD episodes (Correas et al., 2016; López-Caneda et al., 2014b). In these studies, where the subjects were already binge drinkers, the deficits could be reflecting either previous network deficits, the consequences of heavy drinking, or the interaction of both. Our results shed some light to this discussion by indicating an abnormal network organization prior to alcohol consumption, pointing to the presence of early disruptions in executive control networks, indicating a potential vulnerability for BD onset.

The specific mechanism whereby these early unusual FNs organization may occur in first term deserves further remarks for a deeper understanding. One of the neuromaturation events, which could shed light over this question, is the development of mesocortical pathways and its dopaminergic (DA), GABAergic, and glutamatergic (Glu) dynamics during adolescence. The most consistent theories explain adolescent brain maturation as an initial growth of the subcortical "reward system" structures, followed by a posterior development of different cortical regions, such as prefrontal, parietal, and temporal regions, which would exert control over sub-cortical impulsive behaviors as normal maturation advances (Shulman et al., 2016). Thus, eventual neurobiological deviations throughout this neurodevelopmental course, may play an important role in the appearance of problematic consumption behaviors, such BD.

In this matter, the steady growth of works regarding the DA role in the modulation of cortical dynamics takes on special relevance. Among others, one of the most relevant functions of DA pathways over cortical regions is the modulation of GABA inhibitory interneurons (INI), of which parvalbumins (PV) are the most relevant (Caballero et al., 2014).

Table 1
Mean PLV connectivity of significant links.

Links	fLD PLV	fBD PLV	Links	fLD PLV	fBD PLV
'lSFo v. rMotor'	0.816012	0.81597	'lHip v. rFusiG'	0.817461	0.816942
'rMotor v. lSFGmo'	0.815977	0.819294	'lParahip v. rFusiG'	0.817765	0.817111
'rMotor v. lRectus'	0.817139	0.817161	'lRectus v. lSTG'	0.813443	0.813397
'rPreCG v. lACC'	0.813793	0.813008	'rSFG v. rSTG'	0.812059	0.812186
'rMotor v. lACC'	0.824695	0.82647	'rMotor v. rSTG'	0.811381	0.812856
'rMotor v. rPCC'	0.818834	0.817873	'lRectus v. rSTG'	0.812271	0.813379
'rMotor v. lHip'	0.812764	0.813941	'lACC v. rSTG'	0.811901	0.81358
'rIFGt v. rHip'	0.814164	0.81254	'lHip v. rSTG'	0.809806	0.812979
'rMotor v. rHip'	0.813863	0.814561	'rHip v. rSTG'	0.824142	0.824602
'rSFGm v. rHip'	0.81353	0.814526	'lParahip v. rSTG'	0.811219	0.812539
'lACC v. rHip'	0.815354	0.81746	'rHeschl v. rSTG'	0.846505	0.848217
'rACC v. rHip'	0.817925	0.816357	'rMotor v. rMTG'	0.813125	0.81185
'lHip v. rHip'	0.818331	0.822051	'lParahip v. rMTG'	0.812879	0.811957
'rPreCG v. lParahip'	0.810252	0.809666	'rSTG v. rMTG'	0.827786	0.828424
'rSFG v. lParahip'	0.814374	0.812077	'rFusiG v. lITG'	0.815088	0.814787
'rMotor v. lParahip'	0.814214	0.813735	'rMotor v. rITG'	0.813198	0.812586
'rHip v. lParahip'	0.817347	0.822319	'lRectus v. rITG'	0.813408	0.814117
'rMotor v. lLingual'	0.817468	0.812625	'lHip v. rITG'	0.814769	0.81423
'rMotor v. lFusiG'	0.814477	0.811663	'lParahip v. rITG'	0.815268	0.814554
'rMotor v. rFusiG'	0.813991	0.812788	'lITG v. rITG'	0.814024	0.814647

Table 1 shows mean PLV connectivity values for each of 40 significant links. Columns "Links" indicate regions connected for each specific connectivity link. fLD and fBD columns display connectivity values for light drinkers and binge drinkers' groups respectively.

Table 2
Seed-based fc results summary.

Seed	Cluster A (p, sources, cluster alpha)	Cluster B (p, sources, cluster alpha)	Cluster C (p, sources, cluster alpha)
rSMA	0.00005* (OFC, mPFC, ACC, lMTG and lSTG) cluster α 0.01	0.00048* (rTG, rHip, PCC) cluster α 0.01	0.01760 (right somato-motor cortex) cluster α 0.01
ACC	0.0009* (rSMA; right somato-motor cortex) cluster α 0.01	0.01950* (MTG, STG, rHip) cluster α 0.01	0.02470 (lIFG, lMFG, lIns) cluster α 0.01
lHip	0.0096* (rMTG, rSTG, rHip) cluster α 0.01	0.0116* (rSMA, right somato-motor cortex) cluster α 0.01	0.0149* (rHip, rMTG, rSTG, rAng) cluster α 0.01
rIFG	0.0088* (rMTG, rHip) cluster α 0.05		

Table 2 shows p-values for different clusters obtained by Seed-based analysis. Arrows (↑) represent increased FC. The * represent significant clusters which survived Bonferroni's multiple comparison correction. (FC = Functional Connectivity; rSMA = Right Supplementary motor area; ACC = Anterior Cingulate Cortex; IFG = Inferior frontal gyrus; MFG = Medial Frontal gyrus; lHip = Left Hippocampus, lIns = Left Insula; MTG = Medial Temporal gyrus; STG = Superior Temporal gyrus).

The excitation of PV INI releases GABA over pyramidal neurons, inhibiting their activity. In this way, PV INI modulate local and large-scale inhibitory-excitatory balances, on which depend on functional network integrity (Caballero et al., 2016; Tseng and O'Donnell, 2007a). Besides, PV functioning is tied to DA receptor expression, particularly D1 and D2. These receptors follow a progressive maturation along adolescence, becoming functionally effective by early adulthood (Tseng and O'Donnell, 2007b). Consequently, early stages of youth neurodevelopment or its deviations could present several deficiencies in DA neurotransmission and therefore dysfunctional GABA INI activity. This abnormal functioning could cause an inhibitory/excitatory imbalance leading to the hyperconnectivity of FN present in fBDs. In fact, PV INI are disposed in a higher density within Hip, mPFC and ACC, which seem to be the core regions with FC abnormalities detected. The essential role of GABA INI system in the modulation of brain oscillatory activity and cortical networks has been increasingly exposed. A recent biological-based computational work has proved elegantly that the disruption of this INI system causes strong impairment over cortical activity networks (Mongillo et al., 2018) in spite of its lesser proportion (Sahara et al., 2012). Such disturbances could lead to neuropsychiatric and neuropsychological conditions (Di Cristo, 2007; Jupp et al., 2013), reflected in FN anomalies.xº

Beta band is known to be tightly related with motor cortices control, being GABA regulated (Cassim et al., 2001). Moreover, some authors have proposed that beta band represents the maintenance of the cognitive state or "status quo" related with top-down regulation processes (Engel and Fries, 2010; Spitzer and Haegens, 2017). Furthermore, it is suggested that pathological enhancement of beta band synchrony would be related with deterioration of behavioural flexibility and cognitive control (Engel and Fries, 2010). Besides the facts exposed above, the proposed impairment of INI system would be in agreement with previous fMRI findings (Squeglia et al., 2017). As reported by (Niessing et al., 2005; Schölvink, 2010) in interesting studies, hemodynamic dependent signal is highly correlated with the gamma band local synchronization, corresponding to INI populations activity. From this standpoint, the lower BOLD signal found in some of the regions may be related with deficient responses of the INI networks.

As final remarks, complementary lines of research have highlighted the implication of genetic variants of DA-GABA systems in the development of neuropsychiatric and behavioural disorders (Kreek et al., 2005; Verdejo-García et al., 2008) and cortical network disruptions (Di Cristo, 2007; Meyer-Lindenberg et al., 2005). In this regard, the Reward Deficiency Syndrome (RDS) proposed by Blum and colleagues (Febo et al., 2017a) details distinctive genetic, molecular, and neuronal alterations in DA meso-cortical pathways related with the cohort of addictive-fashion habits. Moreover, recently, Febo and colleagues (Febo et al., 2017b), in an extensive review, stated several FC alterations regarding RDS characteristics. Further support to the GABAergic dysfunction hypothesis is found in the deeply studied relationship between AUD disorders and GABRA1 and GABRA2 variations. The last, has been strongly related with higher risk of development alcohol related disorders (Mallard et al., 2018; Porjesz and Rangaswamy, 2007a) and changes in the neurophysiological and neuropsychological endophenotypes. These, are characterized by increased brain oscillatory activity in beta frequency bands, particularly compromising prefrontal networks (Lydall et al., 2011; Porjesz et al., 2002; Porjesz and Rangaswamy, 2007b). Additional evidence has support the role of GABA in the modulation of FC networks, showing a negative relationship between GABA levels and large-scale synchrony (Duncan, 2014).Also, have been reported several differences in personality traits, such as impulsivity, negative affect, behavioural disorders, and neuropsychiatric disorders such ADHD (Villafuerte et al., 2013). With all, behavioural and FN abnormalities found in the present work, may be supported by potential early changes in these neurobiological systems.

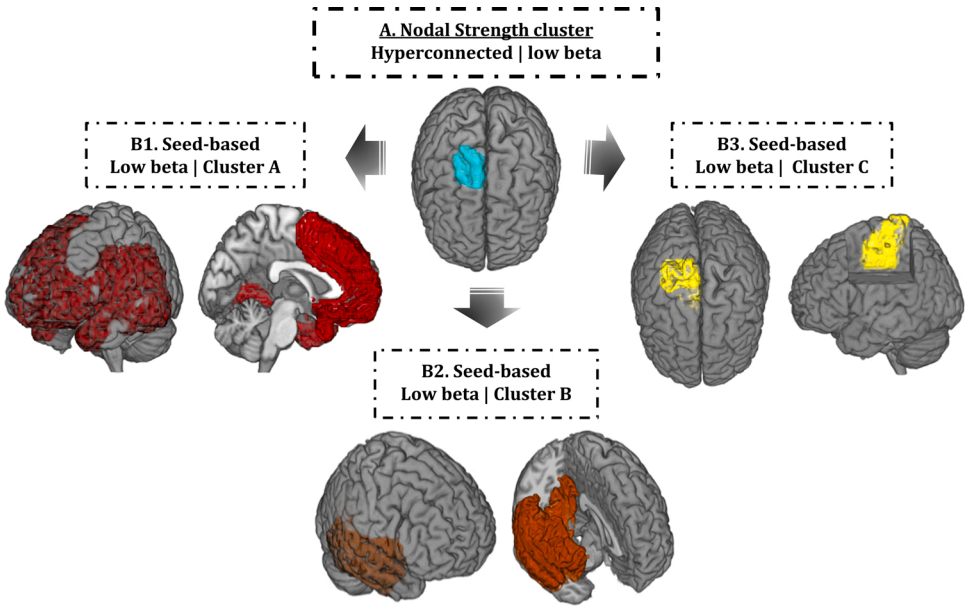

Fig. 4. "Nodal Strength & Strength Seed-Based Results". **(A)** Representation of Nodal Strength results in task inhibitory condition (no-go) at 250 - 350 ms time window. Hyperconnected cluster in low beta band, formed by sources located in rSMA (light blue) ($p = 0.0266$). Using this cluster as Seed, Seed-based analysis showed three independent hyperconnected clusters in low beta band (fBD > fLD): **(B1)** Cluster A (red; $p = 0.00005$); **(B2)** Cluster B (orange; $p = 0.00048$); **(B3)** Cluster C (Yellow; $p = 0.0176$) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

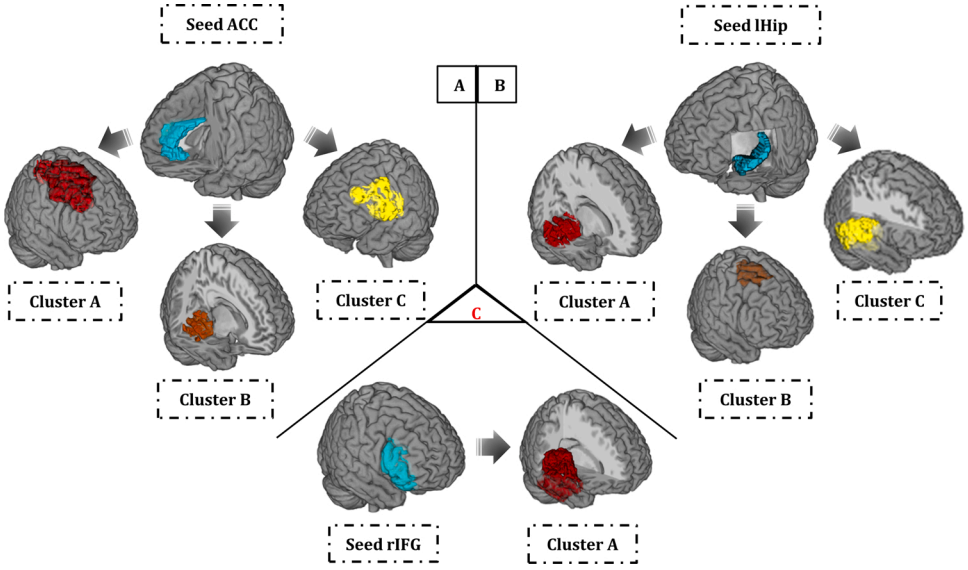

Fig. 5. "Task Rois Seed-Based Results". Representation of AAL ROIs Seed-Based results in task inhibitory condition (no-go) at 250 - 350 ms time window. **A) Seed = ACC (light blue)**: three independent hyperconnected clusters where obtained with cluster alpha 0.01, in low beta band (fBD > fLD): Cluster A (Red; $p = 0.0009$); Cluster B (Orange; $p = 0.0195$); Cluster C (Yellow; $p = 0.0247$*). **B) Seed = lHip (light blue)**: three independent hyperconnected clusters where obtained with cluster alpha 0.01, in low beta band (fBD > fLD): Cluster A (red; $p = 0.0096$); Cluster B (orange; $p = 0.0116$); Cluster C (yellow; $p = 0.0149$). **(C) Seed = rIFG (light blue)**: one independent hyperconnected cluster where obtained with cluster alpha 0.05 in low beta band (fBD > fLD): Cluster A (red; $p = 0.0088$) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

In conclusion, our results provide an important step forward in the understanding of brain's functional synchronization abnormalities as signature of vulnerability towards future substance misuse. We provided, for the first-time, evidence of abnormal neurophysiological functioning of IC networks in alcohol-naïve adolescents before BD initiation, addressed from the point of view of MEG FC networks. Additionally, in the view of FN anomalies, we proposed an achievable and integrative neurobiological framework with the purpose of clarifying the aetiology of this important health and social problem. However, further research will be neccesary to depict the biological basis underlying the neurofunctional anomalies within this population.

Finally, future lines of research should address the genetic variances in this kind of adolescent population from a longitudinal perspective. Such studies are imperative in order to fully understand the relationship between brain's functional abnormalities and neurobiological conditions. Additionally, extensive neuropsychological assessments would help to draw a better profile of those who are more vulnerable to become binge drinkers. Regarding the methodological approach used in this work, PLV has been proved to be highly sensitive to source leakage. In order to overcome this limitation, we performed a series of tests, discussed above and included in the Supplementary results, to identify the level of influence of the phenomenon of source leakage in our results. While it is not possible to completely disregard the possibility of a non-observed influence of this phenomenon, these verifications seem to indicate that this confound is unlikely to drive our results. The analysis of this work was not pre-registered, and the results should be considered exploratory.

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Contributors

All authors of the present work have made substantial contributions to its elaboration. Luis M. García-Moreno, Fernando Maestú and Angeles

Correas designed this research line and outlined main experimental stages. Luis F. Antón-Toro and Luis M. García-Moreno recruited participant's sample, collected data and performed MEG and questionnaires evaluations in both stages of the longitudinal study. Luis F. Antón-Toro, Ricardo Bruña and Isabel Suárez-Méndez, performed MEG data preprocessing and analyses, while Luis F. Antón-Toro and Luis M. García-Moreno analysed data from questionnaires' battery. All authors contributed in the redaction and supervision of this manuscript. Fernando Maestú and Luis M. García-Moreno approved the final version of this work.

Declaration of Competing Interest

Authors of this manuscript do not declare competing interests of any kind regarding current research

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2020.108401.

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