

# Acute alcohol intoxication and expectations reshape the spatiotemporal functional architecture of executive control

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## ABSTRACT

While the deleterious effects of acute ethyl alcohol intoxication on executive control are well-established, the underlying spatiotemporal brain mechanisms remain largely unresolved. In addition, since the effects of alcohol are noticeable to participants, isolating the effects of the substance from those related to expectations represents a major challenge. We addressed these issues using a double-blind, randomized, parallel, placebo-controlled experimental design comparing the behavioral and electrical neuroimaging acute effects of 0.6 vs 0.02 g/kg alcohol intake recorded in 65 healthy adults during an inhibitory control Go/NoGo task. Topographic ERP analyses of covariance with self-reported dose expectations allowed to dissociate their neurophysiological effects from those of the substance.

While alcohol intoxication increased response time variability and post-error slowing, bayesian analyses indicated that it did not modify commission error rates. Functionally, alcohol induced topographic ERP modulations over the periods of the stimulus-locked N2 and P3 components, arising from pre-supplementary motor and anterior cingulate areas. In contrast, alcohol decreased the strength of the response-locked anterior cingulate error-related component but not its topography. This pattern indicates that alcohol had a locally specific influence within the executive control network, but disrupted performance monitoring processes via global strength-based mechanisms.

We further revealed that alcohol-related expectations induced temporally specific functional modulations of the early N2 stimulus-locked medio-lateral prefrontal activity, a processing phase preceding those influenced by the actual alcohol intake.

Our collective findings thus not only reveal the mechanisms underlying alcohol-induced impairments in impulse control and error processing, but also dissociate substance- from expectations- related functional effects.

## 1. Introduction

The association between acute ethyl alcohol intoxication and impulsive behaviors has been advanced to follow from its deleterious effect on executive functions (George et al., 2005; Giancola, 2000; MacDonald et al., 1996). Yet, while this hypothesis is largely supported by behavioral data (Day et al., 2015; Zoethout et al., 2011 for reviews), the underlying spatiotemporal brain mechanisms and the contribution of expectations in the effects of alcohol remain largely unresolved.

Less than ten studies examined the functional correlates of acute alcohol intoxication during executive control tasks in healthy occasional drinkers. Critically, these studies are not only scant, but also involved methods with either limited temporal (fMRI, NIRS) or spatial resolution (event-related potentials) and focused on either stimulus-locked or response-locked activity. These limitations left unresolved whether alcohol impairs feed-forward processes such as attentional capture and stimulus-response mapping and/or later latency conflict detection or top-down motoric inhibition, and hamper the establishment of a global, integrative view of the neurophysiological effects of acute intoxication.

For instance, recent fMRI and NIRS studies showed that alcohol decreases prefrontal and temporal cortex activity, suggesting that impaired executive control and performance monitoring account for the observed disruption of performance (Anderson et al., 2011; Gan et al., 2014; Marinkovic et al., 2012; Tsujii et al., 2011). Event-related potentials studies consistently revealed that acute intoxication reduces inhibition P3 components (Bartholow et al., 2003; Easdon et al., 2005), error processing ERN and Pe components (Bailey et al., 2014; Easdon et al., 2005; Ridderinkhof et al., 2002), as well as evaluative and regulative N450 and NSW components (Curtin and Fairchild, 2003).

In addition, methodological limitations in previous functional studies left unclear whether alcohol induces global quantitative change in brain activity or disrupts specific network sub-components. While the globally depressant GABAergic effect of alcohol would predict effects widely distributed in prefrontal cortices (Valenzuela, 1997), the affinity of alcohol with regionally distributed transmission system would rather predict more circumscribed functional modulations (Abraham et al., 2017).

Finally, current literature did not examine the contribution of alcohol-

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related expectations on the functional effects of alcohol, or only partly controlled for their influence (Anderson et al., 2011; Curtin and Fairchild, 2003; Easdon et al., 2005; Gan et al., 2014; Marinkovic et al., 2012; Tsujii et al., 2011 for studies with single-blinding and/or no placebo control groups; Testa et al., 2006 for review). A major challenge in this regard is to keep participants blind to the intervention; alcohol intoxication has indeed easily noticeable effects, which contributes to generate different expectations depending on the ingested dose.

We addressed these three main questions using a double-blinded, randomized controlled design in which participants performed a Go/NoGo motor inhibitory task after ingesting 0.6 g/kg vs a placebo 0.02 g/kg dose of alcohol. We then applied robust randomization statistics on behavioral measures and on stimulus- and response-locked electrical neuroimaging activity recorded during the task. Electrical neuroimaging involves combining multivariate data-driven analyses of the global power and topographic features of the scalp field potentials with distributed source estimations (Murray et al., 2008; Tzovara et al., 2012). Since ERP power and topography are orthogonal and that topographic changes necessarily follow from alterations in the configuration of the underlying brain generators, this approach allows disentangling selective modulations of network subcomponents from global quantitative variations in the response strength of stable generator configurations. In addition, since EEG directly measures the electric brain activity, source estimations are not biased by alcohol-induced changes in the brain hemodynamic properties, which provides another interpretational advantage over current fMRI data (Pike, 2012).

First, we expected to replicate alcohol-induced impairments in inhibitory control performance (e.g. Ostling and Fillmore, 2010; Tsujii et al., 2011) and post-error slowing (PES, Jedema et al., 2011).

Second, for the functional analyses of executive control processes, we expected an effect over the stimulus-locked 200–350 ms N2 component arising from the anterior cingulate (Huster et al., 2013; Van Veen and Carter, 2002; Yeung et al., 2004). The N2 is sensitive to conflicts between a stimulus-driven response tendency and task demands, as it is the case when a NoGo stimulus prompts for the suppression of a prepotent motor response in Go/NoGo tasks (Nieuwenhuis et al., 2003; Sehlmeier et al., 2010; Wessel et al., 2012). We also expected an effect over the 300–500 ms P3 component (Easdon et al., 2005) arising from lateral and medial prefrontal areas (Huster et al., 2010). The P3 is sensitive to the engagement of the suppression of the motor response to a NoGo stimulus (Ramautar et al., 2004; Wessel and Aron, 2015), suggesting that it indexes the implementation of motor inhibition process and its evaluation (Gajewski and Falkenstein, 2013; Huster et al., 2013; Wessel and Aron, 2015).

For the error detection analyses, we expected an effect over the response-locked 25–75 ms ERN component (Easdon et al., 2005) and the 200–300 ms post-response positivity (Pe) (Easdon et al., 2005), both arising from the anterior cingulate cortex (ACC, Van Veen and Carter, 2002; Yeung et al., 2004).

Regarding whether acute alcohol intoxication has global or regionally specific effects, our approach was mostly exploratory since both hypotheses could be predicted based on previous literature on receptor distributions, and may vary depending on the processing phase of interest.

The effects of alcohol-related expectations were isolated from those of the actual substance intake with an ERP topographic covariance analysis in the placebo group (Koenig et al., 2008). This approach allowed identifying when and where brain activity covary with an external continuous variable, and thus to reveal the functional modulation specifically induced by the amount of alcohol participants believed they had ingested. Since this analysis is conducted in the placebo group only, any observed modulations would be independent of and could thus be dissociated from those of actual intoxication. We hypothesized expectations to influence stimulus-locked activity during the P3 component (Fishman et al., 2008) and/or the lateral and medial prefrontal areas (Gundersen et al., 2008; Ide et al., 2014; Pulido et al., 2015).

## 2. Materials and methods

### 2.1. Participants

Participants were recruited at the University campus and received a financial compensation of CHF 30.- per hour for their participation. Inclusion criteria were: signed informed consent; male; right-handed; French speaking; 18–45 years old; normal body mass index (BMI, ranging from 18.5 to 25 kg/m<sup>2</sup>); occasional alcohol drinker (at least one time per month on average); non-smoker or occasional smoker (maximal regular consumption of five cigarettes daily); and compliance with the preparation procedure (see the Screening section). We recruited only male to control for confounds related to the different metabolism of alcohol in men and women (Baraona et al., 2001; Frezza et al., 1990), and to avoid bias related to interaction between alcohol metabolism and menstrual cycle (Hidalgo-Lopez and Pletzer, 2019; Jacobs and D'Esposito, 2011; Mumenthaler et al., 1999). Exclusion criteria were: consumption of alcohol in the last 24 h before testing; intake of any medication (prescription or not) in the last seven days; history of substance-related addictive or misuse disorders (alcohol or other drugs); personal history of diagnosed neurological or psychiatric disorders; regular consumption of more than 21 units of alcohol/week; history of redness reaction to alcohol or intolerance to moderate doses of alcohol; and Asian ethnicity or ancestry (until great parents, because Asian populations show a high rate of inherited deficiency in the aldehyde dehydrogenase enzymes involved in the breakdown of alcohol).

All experimental protocols were approved by the *Commission cantonale d'éthique de la recherche sur l'être humain* of Lausanne, Vaud, Switzerland, protocol #2017–02128.

A total of 65 participants were recruited for the study (Table 1). One participant was excluded from the EEG analyses due to artifacts-contaminated EEG recording.

### 2.2. General experimental procedure

#### 2.2.1. Participants' screening and instructions

Data were collected in the EEG laboratory of the Neurology Unit of the University of Fribourg, during a unique testing sessions per participant scheduled between 9am and 6pm, either the morning or the afternoon (balanced across groups: 11 OH; 14 PBO for the morning session; 21 OH; 19 PBO for the afternoon session).

Before the beginning of the data collection, participants were instructed that they had to take a regular lunch (or a solid breakfast for the morning sessions) 1.5 h before the appointment and eaten nothing thereafter. They were also instructed to avoid caffeine, nicotine, and drinking anything else than water during this 1.5 h fasting period. Upon arrival at the lab, participants read and signed the informed consent form, and were screened for the inclusion/exclusion criteria. Each eligible participant was then randomly assigned to one of the two experimental conditions (Alcohol, OH or Placebo, PBO) by a collaborator not further interacting with the participant (the experimenters involved in the cognitive testing were blind to the condition assignment). Participants were then told that the study goal was to investigate the effects of

**Table 1**

Population statistics. OH= Alcohol condition, PBO= Placebo condition, SD = standard deviation, BMI= Body Mass Index (kg/m<sup>2</sup>), AUDIT: Alcohol Use Disorders Identification Test (/40), Unit/w = self-reported number of alcohol units per week, Unit/occ = self-reported maximal number of alcohol units per occasion.

Group	Age	BMI	AUDIT	BIS-11	Unit/w	Unit/occ
<b>OH</b> n = 32	25.0	22.4	8.3	59.9	6.9	8.1
Mean (SD)	(4.9)	(1.8)	(3.3)	(8.9)	(4.4)	(4.0)
<b>PBO</b> n = 33	23.9	21.6	7.6	57.6	6.3	7.8
Mean (SD)	(2.6)	(1.8)	(3.6)	(7.7)	(4.6)	(4.5)

alcohol on cognition in a dose response design, and that they will be randomly assigned to a specific dose among several possible doses of alcohol. The participants were informed that none of the laboratory members interacting with them knew which condition they were assigned to, nor the quantity of alcohol in the possible doses, but that the maximal dosage would not exceed 5–6 units of alcohol.

Participants then filled out the following questionnaires: the Edinburgh Handedness Inventory, EHI (Oldfield, 1971); The Barratt Impulsiveness Scale, BIS-11, (Patton et al., 1995); The Alcohol Use Disorders Identification Test, AUDIT (Babor et al., 2001), and a custom General Health Questionnaire, GHQ. They were then instructed on the cognitive testing task and performed a 16 trials familiarization session on the Go/NoGo task. Finally, participants were given the beverage and had to drink it while the experimenter installed the EEG system (see details on exact timing in the subsection Beverage administration).

After the end of the experimental session reported here, participants completed other tasks that will be the focus of future publications.

### 2.2.2. Beverage administration

There were two intervention conditions: The OH condition with a dose of 0.6 g of ethanol/kg of bodyweight and the PBO condition with a dose of 0.02 g of ethanol/kg of bodyweight. Before receiving the beverage, participants' breath alcohol was measured to ensure that their breath alcohol concentrations (BrACs) were initially at 0.00%.

Drinks in the OH conditions were made of 40° white vodka (Absolut®) given at dose 1.875 ml/kg of bodyweight, corresponding to a volume of vodka ranging between 114.4 ml (36.6 gr of ethanol) for our lightest participant (61 kg) and 165 ml (52.8 g of ethanol) for our heaviest participant in the OH condition (88 kg). The vodka was then mixed with  $\frac{2}{3}$  of orange juice (Granini®). Drinks in the PBO condition were made with the same vodka given at a dosage of 0.0625 ml/kg of bodyweight corresponding to a volume of vodka ranging between 3.6 ml (1.2 g of ethanol) for our lightest participant (58 kg) and 5.38 ml (1.7 gr of ethanol) for our heaviest participant in the PBO condition (86 kg). The vodka was then mixed with  $\frac{2}{3}$  of orange juice in a similar proportion as they would have received if they were in the OH condition. The beverages were prepared approximately 5 min in advance. In both experimental conditions, the external collaborator added two sprayings of vodka on the top of the glass just before bringing the drink, to induce a smell of alcohol so that nor the participants nor the experimenters could guess the experimental condition. The administration of the beverage was similar for both OH and PBO conditions: Participants received their drink split in three glasses they had to drink progressively in 7 min each (total drink duration of 21 min). Exactly 15 min after the end of the

drinking session, participants' BrACs and Perceived Alcoholization Scores (two items) were recorded, and the cognitive testing began.

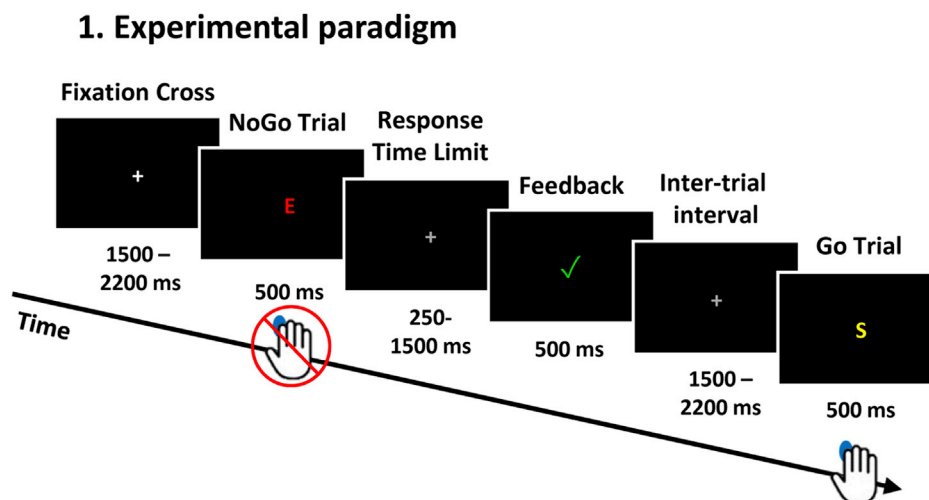
### 2.2.3. Cognitive testing and manipulation checks

Participants were then installed in the EEG testing room and started the Go/NoGo task 15 min after they had finished the beverage. BrACs were recorded in ‰ with a Swiss Dräger Alcotest® 6820 device (where  $0.1‰ \approx 0.01 \text{ g/dL}$ ) before the first and last block of the Go/NoGo task. Two Visual Analogue Scale of 9.5 mm were also given to the participant before the beginning of the Go/NoGo task to assess their self-rated perceived alcoholization ("How do you feel the effects of alcohol right now?" and "How drunk do you feel right now?"). At the end of cognitive testing participants filled out the PEDQ, a custom debriefing questionnaire, assessing the perceived side effects of alcohol and asking them to evaluate the quantity of alcohol they thought they had ingested.

### 2.2.4. Stimuli and tasks

The stimuli and task were the same as in our previous study Hartmann, 2016, except the response time thresholding procedure and the ration of Go and NoGo stimuli (Fig. 1). Visual stimuli were blue, cyan, green, red, white or yellow 'A', 'E', 'M', 'O', 'S' or 'T' letters, centrally presented on a black background. All letter-color combinations were used, for a total of 36 different stimuli. In a given block, NoGo stimuli were either all letters of a given color, or all colors of a given letter (total 12 different NoGo stimuli); Go trials were the remaining stimuli. For example, in a block where the letter "M" was the NoGo stimulus, a total of 20 "M" were presented, and could be written amongst the six possible colors.

Participants were instructed to respond as fast as possible to the Go stimuli by pressing a button on a response box with their right index finger, while withholding their responses to the NoGo stimuli. A total of 4 blocks of 50 trials were completed by each participant, separated by 2 min breaks. Each block consisted of 30 Go and 20 NoGo trials presented randomly. The NoGo stimuli (i.e., a given letter or color) were pseudorandomly chosen across participants so that the same NoGo was never used twice and the order of the NoGo used in each block was different for each participant. Before the beginning of each block, participants were presented with spoken and written instructions about the shape (color/letter) of the block's NoGo stimulus. During the blocks, the median RT was continuously calculated based on the previous correct Go trials to compute a RT threshold (RTt). The RTt was then used as a threshold to provide a feedback on response speed to the Go trials: if the RT to a Go trial was above 110% of the RTt, a feedback 'Too late!' was presented on the screen at the end of the trial. This procedure enabled maintaining the same level of time pressure across participants and blocks, i.e.,



**Fig. 1.** In a given block, NoGo stimuli were either all letters of a given color or all colors of a given letter; Go trials were all the remaining stimuli. A dynamically and individually adjusted response time threshold was implemented to maintain time pressure and response prepotency.

independently of any initial inter-individual differences in Go/NoGo performance (for corresponding procedures, see e.g. Manuel et al., 2010). The feedback on RT thus enabled increasing the tendency to respond when a stimulus was presented and thus the need for inhibition to NoGo trials. Each experimental trial consisted in the presentation of a gray fixation cross on a black screen with a random duration between 1500 and 2200 ms, followed by the stimulus (500 ms) with a response window (1500 ms, fixation cross) terminating as soon as the participant responded, but with a minimal duration of 250 ms. Then, a feedback on the performance was given for 500 ms: a green check mark after Hits (response after a Go stimulus,  $RT < RT_t$ ) or correct rejections (CR, no response after a NoGo stimulus); an orange feedback “Too late!” after hits with a  $RT > RT_t$ ; and a red cross after misses (no response after a Go stimulus) or FA (response after a NoGo trial).

We used the E-Prime 3.0 software (Psychology Software Tools, Inc., Sharpsburg, PA) for stimulus presentation and response recording.

## 2.3. Experimental design and statistical analysis

### 2.3.1. Behavioral analyses

In the Go/NoGo task, we recorded the RT to Go stimuli (correct responses, referred to in the analyses as Hit trials), commission of errors (responding to NoGo stimuli, referred to as false alarm rate, FA rate), and omission error rate (OE rate, no response to Go stimuli).

We analyzed the response speed by fitting an ex-Gaussian curve to each individual's RT distribution (Luce, 1986; Spieler et al., 1996) because of the interpretational advantages of this method (see the Discussion section) and the limitations of usual measures of central tendency to correctly summarize typically skewed RT distributions (McAuley et al., 2006; Parris et al., 2013). We extracted the median and the interquartile range (IQR) of the ex-Gaussian parameters indexing the mean, variability and exponential component (right tail) of the distribution (respectively Mu, Sigma and Tau components). Ex-Gaussian parameters were calculated after the exclusion of the trials with RT below 100 ms. The ex-Gaussian fitting of the RT were conducted with the MATLAB (The MathWorks, Inc., Natick, Massachusetts, USA) script by Bram Zandbelt (2014; <https://github.com/bramzandbelt/exgauss>).

The post-error slowing (PES) was indexed following the procedure by Randles et al. (2016): the difference in the mean RT of Go trials following incorrectly inhibited minus the mean RT of Go trials following correctly inhibited responses to NoGo stimuli. Individuals' mean were calculated after excluding RT below 100 ms and  $\pm 2.5SD$  from the mean.

We verified the assumptions of the parametric ANOVA by exploring the normality of distribution of each behavioral parameter using the Kolmogorov-Smirnov test (Field, 2009), as well as their compliance with a  $\pm 2$  range criterion of skewness and kurtosis (Gravetter and Wallnau, 2013). Since most of our behavioral dependent variables were not normally distributed, we report medians and interquartile ranges (IQR; Table 3; following the recommendations by Habibzadeh, 2013), and submitted all our behavioral dependent variables to non-parametric Mann-Whitney test (Monte Carlo bootstrapping with 10'000 samples using SPSS Statistics 25 software, IBM Corp, Armonk, NY).

Since frequentist analyses cannot provide direct support for null hypotheses, we conducted non-parametric Bayes factors (BF) analyses for each of the effects not reaching our  $p < 0.05$  significance threshold using the open software JASP (JASP Team, 2018; <https://jasp-stats.org/>). Bayes factors express the probability of the data given  $H_0$  relative to  $H_1$  (Dienes, 2011). A  $BF_{01} > 3$  indicates substantial evidence against the effect of alcohol (the data were ca. 3 times more likely observed under the null hypothesis). When non-parametric frequentist analyses were used, we did so for the bayesian analyses and used a Mann-Whitney Bayesian test with 10'000 randomizations and the Cauchy distribution prior set to the default  $r = 0.707$ . Effects sizes are reported using recommendations from Rosenthal (1994) (Rosenthal, 1994);  $r = z \div \sqrt{n}$ , where  $n$  is the total number of samples.

One-sided 95% confidence intervals of the p-value are also reported

for each test. We chose one-tailed tests because all of our behavioral hypotheses were directional.

## 2.4. ERP recording and preprocessing

The 64-channel electroencephalogram was recorded at a sampling rate of 1024 Hz with a Biosemi ActiveTwo system referenced to the common mode sense-driven right leg (CMS-DRL) ground placed on each side of the POz electrode. This circuitry consists of a feedback loop driving the average potential across the montage as close as possible to the amplifier zero (cf. the Biosemi website for a diagram). For the ERP analyses, offline analyses were performed with the MATLAB-based EEGLab toolbox (Delorme and Makeig, 2004) and the Cartool software (Brunet et al., 2011), and statistical analyses were performed with the open toolboxes RAGU (Koenig et al., 2011) and STEN (<http://doi.org/10.5281/zenodo.1164038>).

### 2.4.1. ERP preprocessing

We first referenced the raw data to Cz electrode and applied band-pass filtering between 0.5 and 40 Hz. Then, sinusoidal artifacts (e.g. AC power line fluctuations) and non-stationary signals were removed on the continuous data with the EEGLab plugin CleanLine at 50 and 100 Hz (<https://www.nitrc.org/projects/cleanline>) and Artifact Subspace Reconstruction, respectively (ASR, with settings recommended in Chang et al., 2018; Mullen et al., 2015). Then, for the stimulus-locked analyses, we focused on the correct NoGo inhibition trials: EEG epochs were segmented 100 ms pre-to 700 ms post-stimulus onset and baseline corrected on the whole epochs to correct for any remaining signal drifts. For the response-locked analyses, we focused on the period following Hit (correct Go trials) and False alarms (incorrect NoGo trials): Epochs were segmented  $-200$  ms pre-to 600 ms post-response. We then matched the number of trials included in each ERPs to reach a comparable signal-to-noise ratio across conditions. To this aim, we first determined for each participant separately the condition (Hit or FA) with the lowest number of epochs, and then randomly selected the same number of epochs for the ERP of the other condition (see De Pretto et al., 2016 for a similar approach). The resulting signal was then tested for artifacts by excluding epochs with TF to TF jumps of more than 30  $\mu V$  in at least one electrode and/or epochs with at least one electrode with at least one timeframe with a voltage larger than 80  $\mu V$ . This procedure resulted in, for the stimulus-locked condition:  $63.4 \pm 8.1$  trials (mean  $\pm$  SD) for the OH CR condition;  $64.6 \pm 7.3$  for the PBO CR condition; and for the response-locked condition:  $16.1 \pm 7.9$  for the Hit OH;  $14.8 \pm 7.3$  for the Hit PBO;  $15.6 \pm 7.8$  for the FA PBO;  $14.4 \pm 7.1$  for the PBO. Epochs were then averaged for each and each condition. Once averaged, the ERPs were re-referenced to the common average reference. The ERP for the response-locked condition were then baseline corrected from  $-200$  to  $-50$  ms pre-response to avoid subtracting out the ERN component which typically manifests up to 50 ms before the actual response (Inzlicht and Al-Khindi, 2012). The Hit condition was then subtracted from the FA condition to reveal the error-related components (for a similar procedure see Randles et al., 2016b). Finally, we visually identify bad channel(s) from the averaged ERPs and interpolated them using multiquadric interpolation relying on radial basis functions (see Buhmann and Jäger, 2019; Jäger, 2018; Jäger et al., 2016). An average  $\pm$  SD of  $1.8 \pm 1.9$  electrodes were interpolated for the OH group and  $1.3 \pm 1.6$  for the PBO group in the stimulus-locked conditions and  $2.1 \pm 1.9$  for OH group and  $2.8 \pm 1.7$  for PBO group in the response-locked condition.

## 2.5. Event-related potential analyses

### 2.5.1. General event-related potentials analytical strategy

We first conducted electrophysiological analyses at the local electrode level. This approach entails comparing between the experimental conditions at the level of the ERP waveform for each electrode separately. In contrast, global analyses of the ERP focus on the power and spatial



distribution (i.e. the topography) of the whole electric field at the scalp. Global analyses of the field potentials have the advantage of being independent on the choice of the reference electrode and, as detailed below, of enabling to differentiate effects following from modulations in the strength of the responses of statistically indistinguishable brain generators (i.e. modulations in global field power but not topography) from alterations in the configuration of these generators (i.e. modulations of the topography of the electric field at the scalp; see e.g. Michel and Murray, 2012; or Tzovara et al., 2012 for extensive details on this approach).

### 2.5.2. Local electrode ERP analyses

As a first step, we conducted local electrode analyses by applying the OH vs PBO contrast at each peri-stimulus and peri-response time frame and for each electrode separately with non-parametric t-tests (5000 permutations). Such local electrode analyses actually correspond to the canonical ERP analyses comparing voltage amplitudes for specific ERP components of interest (i.e. the ERP voltage at a given electrode and latency) but extended in time to the whole ERP epoch and space to the whole electrode montage. This analysis has the advantage of allowing to compare our results to those of previous studies based on traditional ERP analyses (for example, our approach could reveal an effect on the classical N2 component by showing a group difference on the typical electrodes and latency of the N2: Frontocentral/anterior electrodes between 250 and 350 ms).

Yet, while this approach is highly sensitive to detect the timing of ERP modulation and thus minimizes the possibility of type II errors, it entails a large number of statistical tests and is thus prone to false positive. In addition, since a change in voltage amplitude can either follow from changes in the strength and/or in the topography of the field potential, local analyses cannot disentangle between the two different underlying neurophysiological mechanisms, and thus have a limited interpretability. For this reason, although we conducted and report these analyses, our interpretations are based on the global analyses of the ERP.

### 2.5.3. Global ERP analyses

Modulations of the strength of the scalp-recorded electric field were analyzed using the global field power index (GFP; Koenig et al., 2011; Koenig and Melie-García, 2010; Lehmann and Skrandies, 1980). GFP is calculated as the spatial standard deviation of the electric field (i.e., the root mean square of the difference between two normalized vectors computed across the entire electrode set). Larger GFP amplitudes indicate stronger electric fields which can arise either from increase in the synchronization or in the extent of the neural sources underlying the scalp-recorded activity (Michel and Murray, 2012).

Modulations of the topography of the electric field at the scalp were analyzed using the global map dissimilarity index (GMD; Lehmann and Skrandies, 1980). GMD indexes differences in the configuration between two electric fields and is calculated as the root mean square of the difference between the potentials measured at each electrode for the different experimental conditions normalized by instantaneous GFP. Because changes in topography forcibly follow from changes in the configuration of the underlying active sources (Lehmann and Skrandies, 1980), topographic modulations reveal when distinct brain networks are activated across experimental conditions.

Since the GFP is insensitive to spatial (i.e. topographic) change in the potential distribution, and that GMD is calculated on GFP-normalized data, the GFP and GMD are orthogonal measures and can thus be interpreted separately.

GFP and GMD were compared across experimental conditions at each time frame using non-parametric randomization statistics (Monte Carlo bootstrapping): the differences in GFP and GMD between the experimental conditions were compared with a distribution of the differences derived from permuting 5000 times the conditions' label of the data for

each participant (Koenig et al., 2011; Murray et al., 2008). The probability of obtaining a GMD and delta GFP values from the permutations higher than the measured value was then determined. The threshold for statistical significance was set at  $p < 0.05$ , and to correct for multiple comparison and temporal autocorrelation we set a minimal duration threshold for a significant effect to be considered. This minimal duration threshold was determined as the shortest duration of consecutive significant time-points that can be expected under the null-hypothesis (shuffled data) with a probability of 0.05 (Koenig et al., 2011; Koenig and Melie-García, 2010; Nichols and Holmes, 2002).

The ERP analyses were used to identify the period of interest showing sustained OH vs PBO difference over which the analysis of source estimations was conducted to identify the origin of these modulations in the brain.

We further conducted a TANCova to identify the global scalp field potentials covarying with participants' expectations on alcohol intake in the PBO group. Because ERP fields are additive, a source proportionally active to an external variable would result in a topographic map that would be added to the ERP. The covariance map can be identified by covarying the external variable with the potentials at each electrode at each time frame of the ERP epoch. Tests for significant covariation are conducted by applying randomization statistics of the GFP of the covariance map (Koenig et al., 2008; and Pedroni et al., 2011 or Sallard et al., 2018 for examples of this approach).

### 2.5.4. Electrical source estimations

Brain sources of ERP modulations were estimated using a distributed linear inverse solution model (a minimum norm inverse solution) combined with the local autoregressive average (LAURA) regularization approach, which describes the spatial gradient across neighboring solution points (Grave de Peralta Menendez et al., 2001; Menendez et al., 2001). LAURA enables investigating multiple simultaneously active sources and selects the configuration of active brain networks that better mimic biophysical behavior of neural fields. LAURA uses a realistic head model, and the solution space included 3005 nodes, selected from a grid equally distributed within the gray matter of the Montreal Neurological Institute's average brain. The head model and lead field matrix were generated with the spherical model with anatomical constraints (SMAC; Spinelli et al., 2000). As an output, LAURA provides current density measures; their scalar values were evaluated at each node. Assessments of the localization accuracy of this inverse solution by fundamental and clinical research indicate that the estimations and the results of their statistical analyses can be confidently interpreted at the resolution of the grid size (here 6 mm; e.g. Menendez et al., 2001; Michel et al., 2004). Yet, given the dependency of the source estimation algorithm to interindividual anatomical differences that were not taken into account in the present study, we conservatively interpret our result with a resolution corresponding to the AAL atlas in which the brain is parcellated into 90 labelled anatomical volume of interest (Tzourio-Mazoyer et al., 2002).

The ERP were averaged for the period of interest determined by the ERP analyses, their sources calculated and then submitted to the same OH vs PBO comparison with randomization statistics as the ERPs (5000 permutations). To correct for multiple testing and spatial autocorrelation, we applied a spatial-extent correction (KE) of  $\geq 15$  contiguous nodes with a  $p$ -value  $< 0.05$ . This spatial criterion was determined using the AlphaSim program (<http://afni.nimh.nih.gov>) and assuming a spatial smoothing of 6 mm FWHM. This program applies a cluster randomization approach. The 10,000 Monte Carlo permutations performed on our lead field matrix revealed a false positive probability of  $< 0.005$  for a cluster greater than 15 nodes.

For the TANCova, since the generated covariance maps consist of a linear transformation of the topographical data, their sources can be directly estimated (Koenig et al., 2008).

### 3. Results

#### 3.1. Manipulation checks

The effects of the interventions are summarized in Table 2 and Fig. 2. Participants in the OH condition exhibited the BrACs that were expected given the 0.6 g/kg dose. They reported higher perceived alcoholization scores and estimated a posteriori having ingested more standard units of alcohol than the participants in the PBO condition who exhibited no alcohol in BrACs (Table 2).

Yet, even if estimations of the quantity and perceived effects of alcohol were larger for participants in the OH condition, our procedure induced important expectations in the PBO group, as indexed by their subjective perceived alcoholization report (31/33 reported a non-null perceived alcoholization, 30/33 estimated having drunk at least 1 standard unit of alcohol, and 32/33 reported at least one alcohol-related side-effect, e.g. concentration deficit, in a post experimental debriefing questionnaire PEDQ).

Our results for RT of ca. 360 ms and false alarm rates of 15–20% during the Go/NoGo task correspond to typical patterns in Go/NoGo tasks and ensure that the task adequately loaded on the inhibitory control component of interest (Wessel, 2018).

#### 3.2. Behavior

The behavioral results are summarized in Table 3 and Fig. 2. As compared to the placebo intervention, the alcohol intake resulted in an increase in the intra-individual RT variability (ex-Gaussian Sigma), an increase in the skewness of the RT distribution (ex-Gaussian Tau), and an increase in PES effect. Bayes factor analyses indicated substantial evidence for an absence of effect of the alcohol on the other behavioral outcomes (FA rate, OE rate and ex-Gaussian Mu); H0 was three times more likely than H1 for these indices of performance (Wagenmakers et al., 2008).

#### 3.3. Event-related potentials

We contrasted the ERP to the inhibition trials for the stimulus-locked analyses and following Hit minus FA for the response-locked ERP between the two groups with robust randomization statistics applied on local ERP waveforms, ERP global field power and topography, as well as on source estimations. We further regressed the expectations on alcohol intake on the ERP in the Placebo group to assess whether participants' expectations influenced the electrophysiological activity.

**Table 2**

Intervention-related measures (n OH = 32, n PBO = 33; Mean (SD) reported). Perceived Alcoholization = mean of two scores of subjective Perceived Alcoholization both measured before the bloc 1 of the Go/NoGo task (Visual Analogue Scale of 9.5 cm: "How do you feel the effects of alcohol right now?") and "How drunk do you feel right now?"); Breath Alcohol Concentration = mean of BrACs before the bloc 1 of the Go/NoGo task and the BrACs after the bloc 3 of the Go/NoGo task, Alcohol Unit Ingested Estimate = number of standard alcohol units that participant think that they had ingested (estimated a posteriori in the post-experimental debriefing questionnaire); M-W U = Mann Whitney U test.

Group	Breath Alcohol Concentration (‰)	Perceived Alcoholization (VAS; 9.5)	Alcohol Unit Ingested Estimate (#)
<b>OH</b>	0.60 (0.16)	4.36 (1.63)	3.50 (1.25)
Mean (SD)			
<b>PBO</b>	0.00 (0.00)	0.97 (0.77)	1.65 (1.09)
Mean (SD)			
<b>OH vs PBO</b>	p < 0.001	p < 0.001	p < 0.001
M-W U			

#### 3.4. Stimulus-locked analyses

The local ERP waveforms analyses identified two main periods of sustained topographic modulations, which were also identified by the global topographic analyses between 220–380 ms and 470–620 ms post-NoGo stimulus onset (Fig. 3;  $p < 0.05$ ;  $> 80$  ms; see the methods section for the interpretation of this minimal duration threshold). There was no period of sustained GFP modulations ( $p < 0.05$ ;  $> 92$  ms).

The statistics on the source estimations localized the origin of the effect during the first period of interest within the anterior cingulate and superior central and left occipital cortices ( $p < 0.05$ ; KE = 15), with a stronger activity in these regions in the OH than PBO group. During the second period of interest the effects were localized within the pre-supplementary (OH < PBO) and anterior cingulate cortices (OH > PBO;  $p < 0.05$ ; KE = 15).

The TANCOVA in the PBO group with the post-experimental estimations of the number of alcohol units the participants thought they had ingested (i.e. the basis of alcohol-related expectations) revealed an effect 170–300 ms ( $p < 0.05$ ;  $> 72$  ms; Fig. 4; we consider the two periods of sustained difference together since they were separated only by a short gap of non-significance period and span during a stable component). This result indicates that the response strength of the network underlying the topographic covariance map covaried with our measure of expectations. A visualization of the sources of the topographical covariations revealed a prominent involvement of the left middle frontal, right inferior frontal and anterior cingulate cortices.

#### 3.5. Response-locked analyses

The local ERP waveforms analyses identified two main periods of sustained topographic modulations, which were also identified by the global topographic analyses between 300 and 530 ms post-response onset (Fig. 5;  $p < 0.05$   $> 51$  ms; see the methods section for the interpretation of this minimal duration threshold) and the global field power analysis between -20–90 ms (OH < PBO;  $p < 0.05$   $> 64$  ms).

The randomization statistics on the source estimations localized the origin of the effect during the earliest period of interest within the cingulate and right temporal pole (OH < PBO;  $p < 0.05$ ; KE = 15). During the latest period of interest, the effects were localized within the left superior frontal gyrus (OH > PBO;  $p < 0.05$ ; KE = 15).

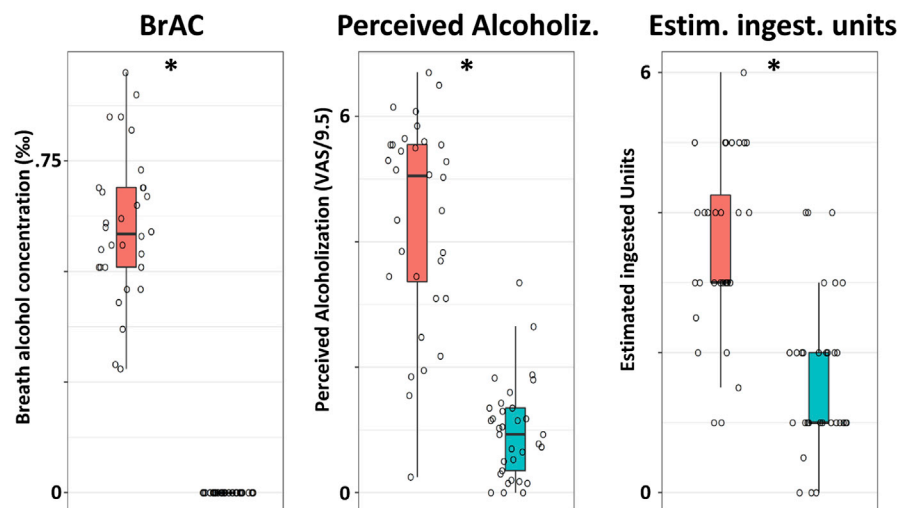
The TANCOVA in the PBO group with the number of alcohol units the participants thought they had ingested revealed no effect.

### 4. Discussion

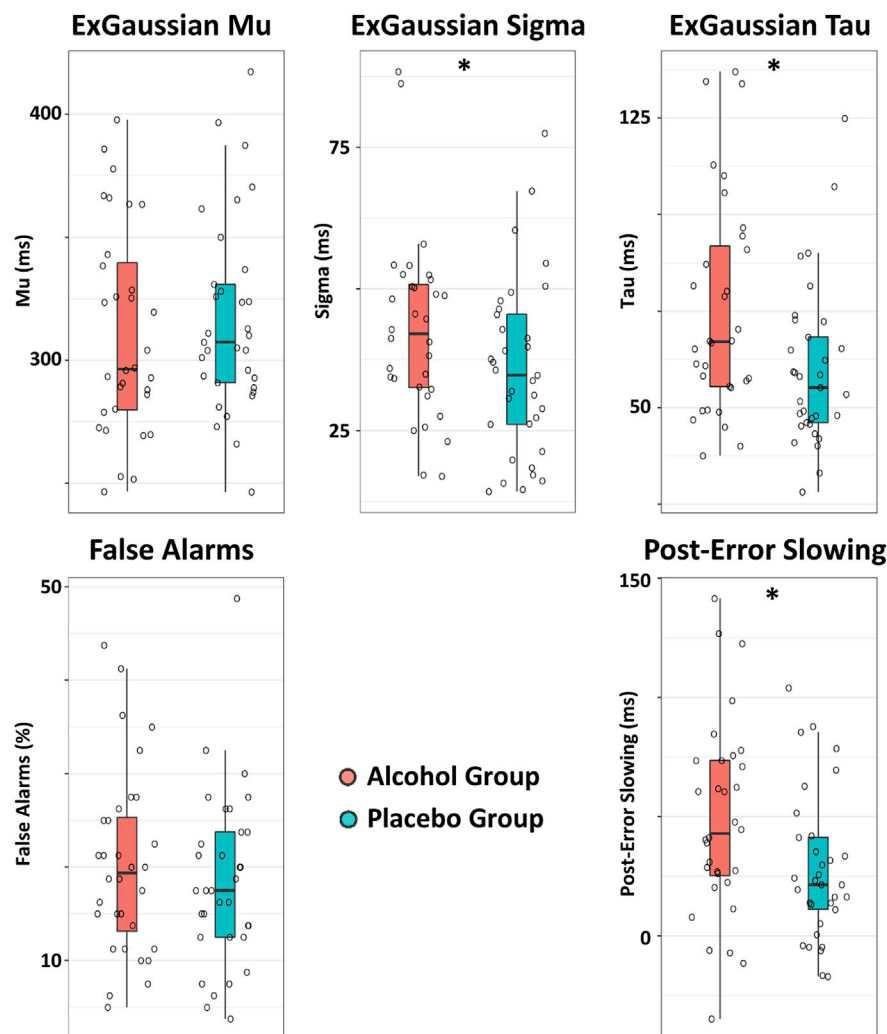
We identified the effects of acute alcohol intoxication and of alcohol-related expectations on the spatiotemporal functional architecture of executive control and monitoring. We used a double-blind randomized control design and robust data-driven randomization statistics on electrical neuroimaging activity during a Go/NoGo task after 0.6 vs 0.02 g/kg alcohol intake. Behaviorally, we found that as compared to the placebo (PBO) condition, the alcohol increased intra-individual RT variability, skewness, and the post-error slowing (PES). Bayes factor analyses confirmed an absence of effect of alcohol on the RT central tendency and commission error rate. Electrophysiologically, the alcohol modulated the ERP topography of the N2 and P3 ERP components, as well as the strength of the ERN and the topography of the late Pe component. Distributed source estimations localized these effects mainly in the anterior medial and central prefrontal areas. This pattern indicates an effect of alcohol on executive control and monitoring process via network- and strength-based mechanisms, respectively. Although we found no influence of alcohol-related expectations on behavioral outcomes, topographic analyses of covariance revealed that they had functional effects, but at a latency earlier than the effect of actual alcohol intake and in medio-lateral prefrontal cortices.

## 2. Behavioral results

### A. Objective and subjective effects of the alcohol and placebo intake



### B. Go/NoGo performance



**Fig. 2.** A. Objectives and subjective effects of the interventions. Group median, IQR and individual data points are represented for the group having received 0.6 g/kg of alcohol (Alcohol group, red) or 0.02 g/kg of alcohol (Placebo group, blue). B. Behavioral results at the Go/NoGo task between the two groups. \*:  $p < 0.05$ .

**Table 3**

Behavioral performance at the Go/NoGo inhibitory control task in the Placebo (OH) and Alcohol (OH) groups. Median (Mdn) and Inter Quartile Range (IQR) are represented, together with Mann-Whitney U statistics comparing the dependent variables between the two groups. 95% Confidence interval for the p-values are also reported, as well as the Bayes factor (BF<sub>01</sub>; likelihood of H<sub>0</sub> over H<sub>1</sub>) for the contrast that did not reach our  $p < 0.05$  significance threshold with the frequentist statistics. \* = parameter of the Ex-Gaussian analyses. FA rate = false alarm rate, operationalization of commission error rate, OE rate = omission error rate.

Behavioral dependent variables	PBO (n = 33) Mdn (IQR)	OH (n = 32) Mdn (IQR)	PBO vs OH contrast (one-tailed Mann-Whitney U, 0.95 p-val CI, Pearson r)
FA rate (%)	17.50 (11.30)	19.37 (14.10)	U = 478.5, z = -0.650, p = 0.26 [0.25 0.27], r = -0.08, BF <sub>01</sub> = 2.09
OE rate (%)	0 (1.70)	0 (0.80)	U = 515.0, z = -0.185, p = 0.43 [0.42 0.44], r = -0.02, BF <sub>01</sub> = 3.84
RT Mu* (ms)	307.42 (44.04)	296.48 (62.64)	U = 471.0, z = -0.748, p = 0.23 [0.22 0.24], r = -0.09, BF <sub>01</sub> = 6.27
RT Sigma* (ms)	34.77 (22.26)	42.08 (18.96)	U = 389.00, z = -1.824, p = 0.03 [0.02 0.03], r = -0.23
RT Tau* (ms)	55.21 (24.33)	67.05 (38.33)	U = 348.00, z = -2.362, p = 0.01 [0.00 0.01], r = -0.30
Post-error slowing (ms)	21.53 (33.53)	43.01 (50.09)	U = 361.00, z = -2.191, p = 0.01 [0.01 0.01], r = -0.27

#### 4.1. Alcohol has limited effects on the Go/NoGo performance

Alcohol increased response time intra-individual variability (Ex-Gaussian Sigma), and skewness (Ex-Gaussian Tau) of the distribution. The Ex-Gaussian fitting approach not only allows overcoming the limitation of means or medians to summarize the central tendency of typically asymmetric RT distributions (McAuley et al., 2006; Parris et al., 2013), but also to decompose them into cognitively distinguishable parameters (Balota and Spieler, 1999; McAuley et al., 2006). The increase in Sigma and Tau components with alcohol suggests that it impaired the maintenance of task goals (Roelofs, 2010; Spieler et al., 1996) and the control of task-related conflict and inhibition (Parris et al., 2013; Roelofs, 2012; Spieler et al., 1996; Steinhäuser and Hübner, 2009).

Bayesian analyses however indicated substantial evidence for an absence of effect of alcohol on the Ex-Gaussian central tendency of the RT and on the rate of commission errors. This result runs counter findings from previous studies with Go/NoGo and Stroop tasks (e.g. Anderson et al., 2011; Field et al., 2010; Fillmore et al., 2009; Marinkovic et al., 2012; Ostling and Fillmore, 2010; Tsujii et al., 2011), which suggests that the behavioral effects of alcohol largely depend on the experimental set-up, tasks or instructions.

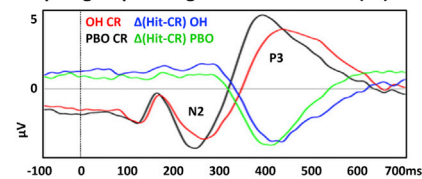
#### 4.2. Alcohol influences the key steps of stimulus-locked executive control process

The electrical neuroimaging analyses revealed that the alcohol modulated the topography but not the strength of the ERP during the periods of the N2 and P3 ERP components. This result speaks against an attentional account of the effect of alcohol on executive control (Bartholow et al., 2003; Gan et al., 2014). First, such effects would have impacted earlier attention-related components as the N2Pc (Luck, 2005) and not later latency components as we observed. Second, lack of focus, diminished motor functioning, or inattentiveness would have manifested as strength- but not network- based mechanisms. Because it influences response gain, variations in attention indeed typically manifest as changes in GFP without concomitant topographic modulations (e.g. Kauramäki et al., 2007).

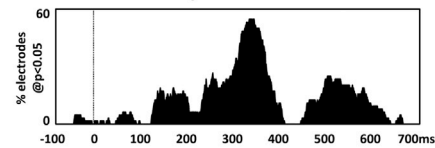
Furthermore, because changes in topographies necessarily follow from modifications in the configuration of the underlying brain

### 3. Electrical Neuroimaging Results: Stimulus-locked OH vs PBO contrast

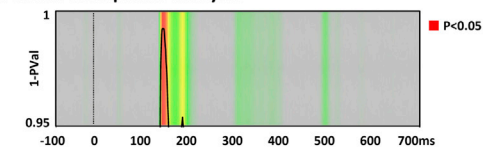
#### A. Exemplar group-averaged ERP waveforms (Cz)



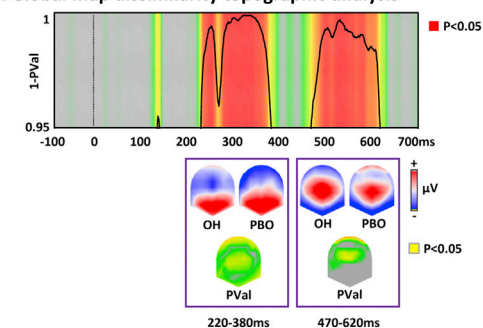
#### B. Local electrodes analysis



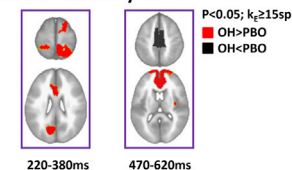
#### C. Global field power analysis



#### D. Global map dissimilarity topographic analysis



#### E. Distributed source estimations analysis

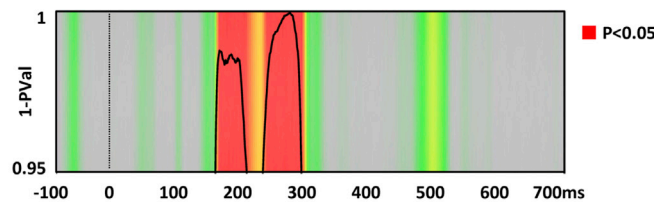


**Fig. 3.** Electrical neuroimaging results for the stimulus-locked event-related potentials analyses to the inhibition trials. A. An exemplar ERP waveform (Cz electrode) confirm the presence of the typical N2 and P3 components. (Hit-CR) difference waveform for the OH (blue) and PBO (green) are also shown. The zero on the time axis corresponds to the stimulus onset. B. Time-wise non-parametric analyses of the Alcohol (OH) vs Placebo (PBO) contrast comparing the ERP voltages across the whole electrode montage revealed two periods of sustained differences around 350 and 550 ms post-stimulus onset, as indexed by peaks in the percentage of electrode showing a difference reaching our  $p < 0.05$  statistical threshold. C. Time-wise non-parametric comparison of the strength of the ERP responses (as indexed by the Global Field Power) revealed no difference reaching our corrected significance threshold ( $p < 0.05 > 92$  ms). D. Time-wise non-parametric comparison of the ERP topography (as indexed by the Global Map Dissimilarity) revealed two periods of sustained differences between ca. 220–380 ms and 470–620 ms post-stimulus onset ( $p < 0.05 > 80$  ms). These effects were mostly driven by differences in central and fronto-central electrodes, respectively (the ERP topographies for each assignment condition averaged over the two periods of interest, as well as the statistical difference between them are represented nasion upward). E. Non-parametric analyses of source estimations averaged over the periods of topographic modulations localized the topographic ERP effects in the pre-supplementary motor area (pre-SMA), anterior cingulate and left precuneus (OH > PBO) for the first period of modulation and within the pre-SMA (OH < PBO) and ACC (OH > PBO) for the second period. KE: minimal cluster size; sp: solution points.

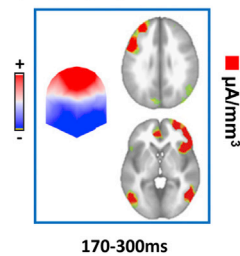


#### 4. Electrical neuroimaging results: Topographic covariance with expectations

##### A. TANOVA with OH-related expectations (PBO group)



##### B. Covariance topography and source estimation



**Fig. 4.** Topographic covariance analyses in the placebo group only with as predictor the number of alcohol units the participants thought they had ingested. A. There was a significant covariance with the topography below the time-wise analysis over the 170–300 ms time period ( $p < 0.05$ ). B. Visualization of the covariance topography and of the underlying sources.

networks, the observed topographic modulation indicates that alcohol modulated selectively some sub-components of the executive network, instead of merely inducing global quantitative decreases in the whole network activity. Although speculative, this pattern suggests that the functional effects of alcohol primarily depend on transmission systems with receptor concentrated on specific part of the executive network such as the dopaminergic system (e.g. Levey et al., 1993). In contrast, an effect mediated by widespread GABA receptors would have preferentially manifested as a changes of global network response gain and thus resulted in a GFP modulation (Sivilotti and Nistri, 1991; Waldvogel et al., 2010).

The source estimations revealed a larger anterior cingulate and centro-parietal activity in the alcohol compared to placebo group over the late N2 period. This result is consistent with previous evidence for a source of the N2 in the ACC (Van Veen and Carter, 2002; Yeung et al., 2004), and effect of alcohol on this area (Anderson et al., 2011; Marinkovic et al., 2012). However, the direction of the effect runs counter previous observations for decrease in ACC activity during Go/No-Go and Stroop tasks (Anderson et al., 2011; Marinkovic et al., 2012). Given the low temporal resolution of fMRI, the dynamic changes in single brain regions occurring within the millisecond range might have been mixed with other parallel activity (Ghuman and Martin, 2019). In addition, hemodynamic investigations of the effect of alcohol might be confounded by its vascular effects (Pike, 2012). Hence, while ACC activity might be overall increased across the multiphase executive process, we could identify that during the response-conflict detection N2 and inhibition P3 phases, alcohol actually increased the engagement of the ACC. More resources may thus be required to monitor and solve task-induced response conflicts after alcohol intake. Likewise, the increase in centro-parietal areas activity during the N2 suggests that the alcohol may have increased the demand for stimulus-response mapping rule integration (Logan, 1988; Shiffrin and Schneider, 1977). Centro-parietal areas have indeed been involved in the sensory to motor coordinates transformation (Andersen et al., 1997), as well as in movement preparation (Decety et al., 1992; Deiber et al., 1991). This hypothesis is in line with previous data for impaired movement selection after intoxication (Van Horn et al., 2006).

Finally, we observed a decrease in pre-SMA activity with alcohol during the P3 inhibition phase. This region is a key node of the motor

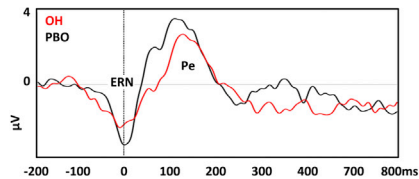
inhibitory control network, acting together with the right inferior gyrus to implement the inhibition command (Sharp et al., 2010; Swann et al., 2012; Zandbelt et al., 2013). Alcohol thus also impact proper inhibition processes, but not primarily those related to the triggering of the inhibition command in ventrolateral prefrontal areas (Aron et al., 2014).

#### 4.3. Alcohol influences the key steps of response-locked performance monitoring process

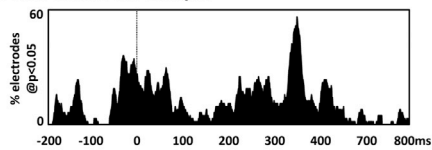
Contrasting with previous observations for an absence of effect of alcohol on PES (Easdon et al., 2005; Marinkovic et al., 2012, though see Jedema et al., 2011 for contradicting data in non-human primates), we found larger increase in the RT following the commission of errors in the OH than PBO group. Increases in the PES could be interpreted either as a strategic increase in response threshold after commission errors (Botvinick et al., 2004) or as reflecting a difficulty in reorienting attention to the task after the detection of infrequent errors (Bailey et al., 2014; Easdon et al., 2005; Ridderinkhof et al., 2002). The orienting account is in line with our finding for alcohol-induced changes in the GFP but not the topography of the ERN response-locked component. This pattern indeed indicates that the intoxication decreased the strength of the error-related activity, but did not alter the configuration of the underlying network. The ERN has been advanced to index the detection of a need for executive control and its subsequent implementation, notably when strategic readjustments -such as shifts of attentional focus-are required after errors (Gehring et al., 1993). As in our result, most of previous literature localized the source of the ERN within the cingulate cortices, very close to the pre-SMA (e.g. Holroyd and Coles, 2002; with authors reporting the source in the dorsal ACC: Holroyd et al., 2004; Van Veen and Carter, 2002; Yeung et al., 2004; and others in the rostral cingulate cortex: Debener, 2005; Ridderinkhof et al., 2004). A decrease in ERN seems incompatible with larger PES because a disruption of error detection should be associated with smaller (and not larger) effects of error commission on the subsequent trials RT. Our finding for a sustained topographic modulation during the late error positivity (Pe) component possibly reconciles these apparently opposing results (see Overbeek et al., 2005, for review): While the late positivity is typically larger when participants are aware of their error (Endrass et al., 2005), it may also represent a P300-like attentional reorienting response (Arbel and

## 5. Electrical neuroimaging results: Response-locked OH vs PBO contrast

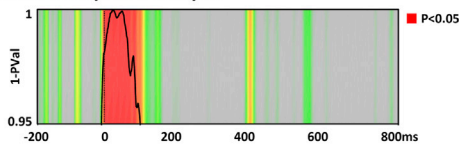
### A. Exemplar group-averaged FA-Hit difference ERP waveforms (FCz)



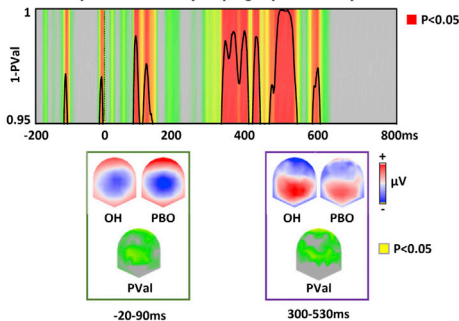
### B. Local electrodes analysis



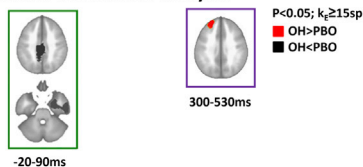
### C. Global field power analysis



### D. Global map dissimilarity topographic analysis



### E. Distributed source estimations analysis



**Fig. 5.** Electrical neuroimaging results for the response-locked event-related potentials analyses on FA minus Hit trials between the OH and PBO group. A. An exemplar difference (FA-Hit) ERP waveform (FCz electrode) confirms the presence of the typical ERN and Pe components. The zero on the time axis corresponds to the motor response. B. Time-wise non-parametric analyses of the Alcohol (OH) vs Placebo (PBO) contrast comparing the difference ERP voltages across the whole electrode montage revealed two periods of sustained differences around 100 ms and 500 ms post-response onset, as indexed by peaks in the percentage of electrode showing a difference reaching our  $p < 0.05$  statistical threshold. C. Time-wise non-parametric comparison of the strength of the ERP responses (as indexed by the Global Field Power) revealed stronger field strength in the PBO vs OH condition  $-20$  to  $90$  ms peri-response ( $p < 0.05$   $> 64$  ms). D. Time-wise non-parametric comparison of the ERP topography (as indexed by the Global Map Dissimilarity) revealed a sustained difference between ca.  $300$ – $530$  ms post-response ( $p < 0.05$   $> 51$  ms). These effects were mostly driven by differences in central electrodes, respectively (the ERP topographies for each assignment condition averaged over the two periods of interest, as well as the statistical difference between them are represented nasion upward). E. Non-parametric analyses of source estimations averaged over the periods of GFP and topographic modulations localized the GFP ERN effects in the dorsal cingulate and right temporal pole (OH < PBO) and the topographic Pe modulation within the left superior frontal gyrus (OH > PBO). KE: minimal cluster size; sp: solution points.

Donchin, 2009). Accordingly, disrupted error detection might have led to a less efficient engagement of reorientation processes and in turn in larger PES. The localization of the effect in the left superior frontal gyrus is consistent with this hypothesis given the involvement of this area in attentional orienting (Corbetta and Shulman, 2002). In that sense, the pattern of response-locked ERP modulations, together with the increased PES in the OH group might also account for the observed absence of difference in the rate of inhibition failure between the two group: The larger slowing down after errors in the OH group might have resulted in a decrease in error commission.

#### 4.4. Alcohol-related expectations do not impact performance, but modulate early latency executive functional activity

The important perceived alcoholization and estimated ingested dose in the PBO group confirmed the efficacy of our procedure to keep the participants naive to their actual alcohol intake. Yet, these values were still lower in the PBO than in the OH group, indicating that expectations might have confounded our main contrast of interest. Speaking against this hypothesis, we did not find any associations between the behavioral performance and the expectations (suppl. table 2), and our topographic covariance analysis indicated that expectations did not influence functional activity over the periods showing the OH vs PBO ERP difference. Yet, we found that the amplitude of the expectations covaried with the earlier  $150$ – $300$  ms latency anterior cingulate and left superior frontal activity; hence, while alcohol expectancies might only have small effects on executive motor control performance (Hull and Bond, 1986; Testa et al., 2006), they still induced measurable functional effects. The  $150$ – $300$  ms latency corresponds to the period of the beginning of the N2 component, a processing phase encompassing attentional selection ‘gain-control’ processes (Matusz et al., 2018) and the detection of the response conflict (Donkers and van Boxtel, 2004). The localization of our modulation is also consistent with previous findings for modulations in medial and dorsolateral prefrontal areas by substance-related expectations (Benedetti et al., 2011; Petrovic et al., 2002; Wager et al., 2004; Zubieta, 2005). Importantly, this observation calls for very cautious interpretations of functional results for an effect of alcohol on the N2 ERP component and/or anterior cingulate activity when experimental designs do not strictly control for expectations. We would finally note that we cannot exclude that our effect was driven by common factors, such as individual traits, influencing both expectancies and inhibitory control processes.

#### 4.5. Converging effects of acute and chronic alcohol intoxication?

Our general findings on the effect of acute alcohol intoxication echo current evidence for the anatomo-functional modifications of executive control associated with long-term alcohol abuse. This literature indeed indicates that heavy drinkers exhibit poorer performance and altered prefrontal activity during Go/No-Go inhibitory control tasks. For example, Ames et al. (2014) observed that higher activity in the right dorsolateral prefrontal cortex, anterior/mid cingulate cortex and right anterior insula during the NoGo trials in heavy drinkers, a pattern of results corresponding both spatially and in terms of the direction of the effect to the pattern observed in our study. Ahmadi et al. (2013) also reported that heavy drinkers change in inhibition-related activity in the ACC, portions of frontal lobe, superior temporal regions, hippocampus and thalamus, though in a reverse direction. In addition, ERP studies using Go/No-Go tasks comparing alcohol-specific cues also identified differential neural correlates of poorer inhibitory control performance in heavy drinkers (Blanco-Ramos et al., 2019; Petit et al., 2012). While these studies could not determine whether these altered functional patterns reflect dysfunction or compensatory mechanisms (Campanella et al., 2017), they suggest, together with our study, that partly overlapping areas are sensitive to acute and chronic alcohol intake.

#### 4.6. Limitations

Our study suffers several limitations. First, we did not include an analysis of the Go trials in the Stimulus-locked investigations. As a consequence, we could not conclude on the specificity of the observed effects on the inhibition processes, but only that alcohol intoxication *at least* influences inhibitory control as we demonstrated. A test for the specificity of the effect of alcohol on inhibition would have required using a Condition (Go; NoGo) by Group (PBO; OH) design. We could not do so because the frequency of the Go and NoGo condition was not balanced (we included more Go than NoGo to increase response propensity and thus the demand for inhibition). As a result, any Condition by Group interaction would have been confounded by differences in exposure.

Second, the choice for a between-subject design had for disadvantage that we could not rule out that pre-existing differences between groups account for our results. Yet, the randomization procedure we used, together with our rather large sample size and the homogeneity of our population, minimized the influence of population-related confounds. In addition, the choice for a between-subject design allowed a better blinding of the participants since they did not experience each condition (and thus could not compare them to infer the actual doses they were given) and for a control of test-retest effects.

Finally, we could not conclude on a putative relationship between the effects found at the level of the N2 vs P3 component. Future studies varying parametrically the task features known to differently impact on each of these components are required to identify whether and how alcohol may influence their interactions.

#### 4.7. Conclusion

Our collective results provide robust and comprehensive evidence that the functional effects of alcohol manifest at each of the key step of the executive control and monitoring process and localize them in time and space. They further reveal that alcohol influences executive processes via locally specific network sub-component influence for the stimulus-locked activity, and quantitatively for the error-related response-locked activity, suggesting the involvement of transmission systems with regional and widespread distributions, respectively.

We further circumvented the impossibility for blinding participants to the intake of substance with noticeable effects and reveal that expectations influences anterior cingulate response conflict and attention-related activity even if it does not influence behavioral outcomes. This result not only indicates a dissociation of the functional effects of expectations from those of actual alcohol-intake, but also suggests that previous results for alcohol-induced modulations during this processing step and brain areas might have been confounded by expectations.

#### Author contributions section

Farfalla Ribordy Lambert: Conceptualization; Methodology; Investigation; Formal analysis; Writing - Original draft preparation; Writing - Review & Editing.

Corentin Wicht: Software; Formal analysis.

Michael Mouthon: Software; Investigation.

Lucas Spierer: Project administration; Conceptualization; Methodology; Writing - Original draft preparation; Supervision; Funding acquisition; Writing - Review & Editing.

#### Declaration of competing interest

The authors declare no conflict of interest.

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#### Appendix A. Supplementary data

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