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ALCOHOLISM CLINICAL & EXPERIMENTAL RESEARCH

RESEARCH ARTICLE

Theta oscillatory dynamics of inhibitory control, error processing, and post-error adjustments: Neural underpinnings and alcohol-induced dysregulation

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Abstract

Background: Alcohol intoxication impairs inhibitory control, resulting in disinhibited, impulsive behavior. The anterior cingulate cortex (ACC) plays an essential role in a range of executive functions and is sensitive to the effects of alcohol, which contributes to the top-down cognitive dysregulation. This study used a multimodal approach to examine the acute effects of alcohol on the neural underpinnings of inhibitory control, inhibition failures, and neurobehavioral optimization as reflected in trial-to-trial dynamics of post-error adjustments.

Methods: Adult social drinkers served as their own controls by participating in the Go/NoGo task during acute alcohol and placebo conditions in a multi-session, counterbalanced design. Distributed source modeling of the magnetoencephalographic signal was combined with structural magnetic resonance imaging to characterize the spatio-temporal dynamics of inhibitory control in the time-frequency domain.

Results: Successful response inhibition (NoGo) elicited right-lateralized event-related theta power (4 to 7 Hz). Errors elicited a short-latency increase in theta power in the dorsal (dACC), followed by activity in the rostral (rACC), which may underlie an affective "oh, no!" orienting response to errors. Error-related theta in the dACC was associated with subsequent activity of the motor areas on the first post-error trial, suggesting the occurrence of post-error output adjustments. Importantly, a gradual increase of the dACC theta across post-error trials closely tracked improvements in accuracy under placebo, which may reflect cognitive control engagement to optimize response accuracy. In contrast, alcohol increased NoGo commission errors, dysregulated theta during correct NoGo withholding, and abolished the post-error theta enhancement of cognitive control.

Conclusions: Confirming the sensitivity of frontal theta to inhibitory control and error monitoring, the results support functional and temporal dissociation along the dorso-rostral axis of the ACC and the deleterious effects of alcohol on the frontal circuitry subserving top-down regulation. Over time, alcohol-induced disinhibition may give rise to compulsive drinking and contribute to alcohol misuse.

KEYWORDS
alcohol intoxication, anterior cingulate cortex, errors, event-related theta, response inhibition

INTRODUCTION

Inhibitory control refers to the ability to deliberately withhold or stop already initiated habitual or prepotent responses. It is a fundamental aspect of executive functions and is engaged in the service of flexibly executing and suppressing responses in a manner that is goal-directed and adapted to the relevant contextual demands. Deficits in inhibitory control are an essential feature of a range of brain-based disorders including addiction (Weafer et al., 2014). Numerous neuroimaging studies have reported that inhibitory control engages a distributed activation pattern. It includes the cortices subserving motor execution and inhibition such as sensorimotor (sMOT), pre-supplementary (pre-SMA), or supplementary motor areas (SMA) but also other areas associated with attention, working memory, monitoring for errors, and response optimization functions needed to perform the task. These comprise the right-dominant medial and lateral frontal, parietal, and lateral temporal areas (Aron et al., 2014; Criaud & Boulinguez, 2013; Happer et al., 2021; Wessel, 2018a). While the SMA and pre-SMA are involved in response inhibition, activation often extends into more anterior medial frontal areas including the dorsal anterior cingulate cortex (dACC), especially under the conditions of increased task difficulty (Nachev et al., 2008; Rosen et al., 2016). Because it is activated by a range of tasks and conditions, the dACC is considered to be an essential hub in the "core" task set subserving different facets of cognitive control including conflict monitoring, response selection, valuation, salience appraisal, task-set representations, and behavior optimization (Heilbronner & Hayden, 2016; Kolling et al., 2016; Sheth et al., 2012).

Inhibitory Go/NoGo task variants are designed to induce a propensity for responding to frequently presented Go trials that prime response readiness. In contrast, responses must be withheld to randomly interspersed, infrequent NoGo stimuli, which amplifies the need to inhibit the prepotent response set (Garavan et al., 2002; Wessel, 2018b). As a result, NoGo trials often induce rather high rates of inhibitory control failures and are well suited for examining error monitoring and post-error adjustments. Error monitoring is an important aspect of cognitive control that underlies behavioral optimization within adaptive feedback loops (Wessel, 2018a). Post-error adjustments have been variably interpreted as resulting from increased cognitive control processes related to error occurrence (Ridderinkhof et al., 2004), increased inhibitory motor processes (Danielmeier & Ullsperger, 2011), or attentional re-orienting due to the oddball nature of errors (Wessel, 2018a). An example of such an adjustment is post-error slowing (PES), which is reflected in longer reaction times on post-error trials compared with those following successful inhibition (Danielmeier & Ullsperger, 2011; Wessel, 2018a). In agreement with the cognitive control account, neuroimaging evidence indicates that the medial and lateral prefrontal cortices are engaged during post-error adjustments (Ullsperger et al., 2014). The dACC has been implicated in performance monitoring, response selection, and post-error adjustment via the top-down influence, and through interactions with the lateral prefrontal cortex (Marinkovic et al., 2019; Ullsperger et al., 2014). In addition, error-related activity commonly extends to the rostral ACC (rACC), also termed pregenual ACC, which has been associated with evaluation of the affective or motivational significance of errors in the context of cognitive control, mediated by its direct connections with limbic structures and other medial and lateral frontal areas (Tang et al., 2019). The ACC is engaged during high conflict and error trials across different cognitive control tasks and response modalities and is particularly vulnerable to alcohol intoxication (Anderson et al., 2011; Marinkovic et al., 2012a; Marinkovic et al., 2013), which is consistent with alcohol-induced impulsivity and reduction of self-control (Anderson et al., 2011; Bartholow et al., 2003; Curtin & Fairchild, 2003; Field et al., 2010; Loeber & Duka, 2009; Marinkovic et al., 2000).

Contributions of different brain regions to inhibitory control and error processing have been examined extensively with functional magnetic resonance imaging (fMRI). However, even though the fMRI method is an excellent spatial mapping tool, it reflects regional blood flow and oxygenation changes mediated by neurovascular coupling (in seconds), and is unable to track a much faster temporal scale of neural activity (in milliseconds). Importantly, due to its hemodynamic nature, fMRI is not well suited for studying the effects of acute intoxication on neural activity since the signal is affected by alcohol's vasoactive properties (Rickenbacher et al., 2011). In contrast, electroencephalography (EEG) reflects postsynaptic currents directly. EEG-derived event-related potentials are highly sensitive to temporal stages of alcohol-induced error-related processing and post-error adjustments, with an emphasis on error-related negativity (ERN; Bailey et al., 2014; Bartholow et al., 2012; Cofresi & Bartholow, 2020; Holroyd & Yeung, 2003; Ridderinkhof et al., 2002). Magnetoencephalography (MEG) is a related technique that measures the magnetic fields generated by synaptic currents, ensuring its excellent temporal resolution. The present study used an anatomically-constrained MEG (aMEG) method which combines distributed source modeling of the high-density MEG signal with structural MRI in a multimodal approach. Each participant's reconstructed cortical surface serves to constrain the inverse solution based on the assumption that the synaptic currents are generated in the cortical gray matter (Dale et al., 2000). This method makes it possible to elucidate the spatio-temporal characteristics of inhibitory control, error, and post-error processing as they unfold under pharmacological influence of alcohol (Beaton et al., 2018; Kovacevic et al., 2012; Marinkovic et al., 2012b; Marinkovic et al., 2014; Rosen et al., 2016). Event-related theta oscillations have been established as an index of cognitive control, novelty, and task difficulty (Cavanagh & Frank, 2014; Rosen et al., 2016). Error monitoring and post-error

adjustments are reflected in theta dynamics, which subserves long-range cortical synchrony essential for cognitive control (Beaton et al., 2018; Cavanagh & Frank, 2014; Cohen, 2016; Marinkovic et al., 2019; Wang et al., 2005). Furthermore, theta oscillations are highly (Kovacevic et al., 2012; Marinkovic et al., 2012b) and selectively (Beaton et al., 2018) sensitive to acute alcohol intoxication. Therefore, the present study examined the effects of acute alcohol intoxication on inhibitory control as reflected in: (1) spatio-temporal dynamics of theta oscillations during a Go/NoGo task, (2) error processing in the prefrontal cortex, and (3) trial-to-trial behavioral and neural dynamics of post-error adjustments with an emphasis on the ACC.

MATERIALS AND METHODS

Participants

Sixteen healthy volunteers (eight women, average age 29.2 ± 5.6 years) successfully completed all four sessions of this multimodal imaging study. All were right-handed non-smokers, with no medical, alcohol or drug-related problems, no previous head injuries, or MRI contraindications. They all reported a negative family history of alcohol or drug abuse, and were not taking any medication at the time of the study. Participants reported drinking alcohol occasionally (~1.6 ± 1.0 times a week), mostly in social settings and at low-risk levels (~2.3 ± 0.8 drinks per occasion). They had no alcoholism-related symptoms as assessed with Short Michigan Alcoholism Screening Test (SMAST; Selzer et al., 1975). One additional participant took part in the study, but was excluded due to low behavioral performance. All gave written informed consent approved by the Human Research Protections Programs at the University of California at San Diego and San Diego State University, and were compensated for their participation.

Experimental design and procedure

A within-subject design was used to minimize the influence of individual differences in anatomy and brain activation patterns. Each participant took part in four sessions: an introductory MEG familiarization session, counterbalanced alcohol and placebo beverage MEG sessions, and an MRI scan. In total, we conducted 64 sessions for this group of participants. During the no beverage acclimation session, participants were familiarized with the experimental procedure by practicing the task during a mock recording. This helped abate potential effects of situation-induced arousal and ensured balanced comparison between the alcohol and placebo sessions. Participants provided information on their health status and alcohol related history, including consumption levels and severity of alcohol-related symptoms (SMAST; Selzer et al., 1975), and completed the Eysenck Personality Questionnaire—revised form (Eysenck et al., 1985).

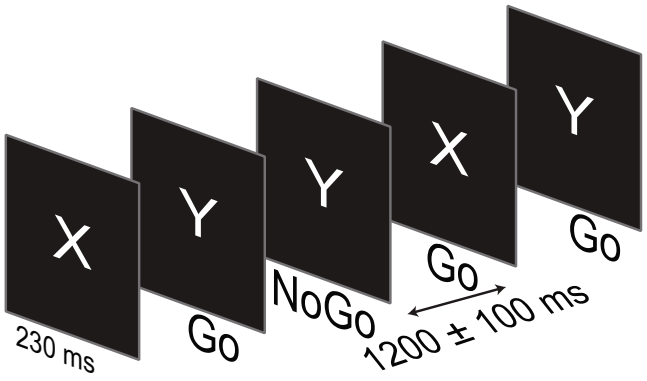

FIGURE 1 Inhibitory Go/NoGo task. A sequence of "X" and "Y" letters, 600 in total, was presented in rapid succession every 1200 ± 100 ms. Each letter was presented for 230 ms and was replaced by a centrally located fixation dot for the remainder of the trial. Participants were instructed to respond with their right index finger to each alternation (Go, 80%) and to inhibit responding to each letter repetition (NoGo, 20%). In this task, all NoGo errors are errors of commission, and all Go errors are errors of omission

Subsequently, participants took part in alcohol and placebo sessions that were counterbalanced on two different days. They abstained from drinking for ≥48 h and from food for ≥3 h prior to each experiment. All multi-drug screens (Discover, American Screening Corporation) and pregnancy tests for women were negative. In the alcohol session, participants were given alcohol (0.60 g/kg for men, 0.55 g/kg for women), presented as a cocktail containing 20% v/v vodka (Gray Goose, Bacardi) in orange juice. In the placebo session, the same volume of orange juice was served with a few drops of vodka (Kovacevic et al., 2012; Marinkovic et al., 2012b). Breath alcohol concentration (BrAC) was measured with a breathalyzer (Alcotest 7410, Draeger Inc.) while participants were outside the recording chamber. Since no electronic device can be used in the magnetically shielded room, Q.E.D. Saliva Alcohol Test (OraSure Techn, Inc.) was used during the recording. Participants rated their moods and feelings with the Biphasic Alcohol Effects Scale (Martin et al., 1993) at baseline on arrival, on the ascending BrAC limb, and at the end of the experiment, on the descending BrAC limb. The BrAC levels averaged at 0.060 ± 0.015% before, and 0.050 ± 0.009% after the task, suggesting that the task performance overlapped with the peak and the early portion of the descending BrAC limb. At the end of each session, participants rated their intoxication levels and task difficulty. Transportation to and from home was provided. High-resolution structural MRI scans were obtained from all participants in a separate session.

Go/NoGo task

A visual Go/NoGo task (Garavan et al., 2002; Holcomb et al., 2019) consisted of a series of "X" and "Y" letters presented in rapid succession every 1200 ± 100 ms (Figure 1). The stimuli were presented for 230 ms as white letters on a black screen and were replaced by

a fixation dot for the remainder of the trial. Participants were instructed to press a single button to each alternation of "X" or "Y" with their right index finger ("Go", 80%), but to withhold their responses to each letter repetition ("NoGo", 20%). Therefore, in this task, all NoGo errors are errors of commission and all Go errors are errors of omission. A total of 600 stimuli were presented using Presentation software (Neurobehavioral Systems), while participants' responses were collected.

Data acquisition and analysis

MRI

Structural MRI images were acquired with a 1.5 T GE EXCITE HG whole-body scanner (General Electric) with two high-resolution T1–weighted IR-FSPGR scans that were used to reconstruct each person's cortical surface. The inner skull surface was used for a boundary element model of the volume conductor in the forward calculations. Each participant's reconstructed gray-white matter surface was morphed onto an average representation and served as the solution space for inverse estimates (Dale et al., 2000).

MEG

MEG signals were recorded with a whole-head Neuromag Vectorview system (Elekta) in a magnetically and electrically shielded room (Imedco). Measurements were obtained continuously from 204 gradiometers with 1000 Hz sampling rate and minimal filtering (0.1 to 330 Hz). Positions of the four head-position indicator coils, the main fiducial points, and a large array of additional head points were digitized to allow for precise co-registration with MR images. MEG data were band-pass filtered from 0.5 to 100 Hz and epoched from −800 to 1250 ms. Artifacts were removed by threshold-based automatic rejection procedure followed by visual inspection. Independent component analysis (Delorme & Makeig, 2004) was used to remove heartbeat and eye blink artifacts. The continuous Morlet wavelet transform was applied to single trial epochs in 1 Hz increments for theta band frequencies (4 to 7 Hz; Kovacevic et al., 2012; Marinkovic et al., 2012b). Padding was discarded to remove edge artifacts produced during the wavelet transform, resulting in −300 to 800 ms epochs. Source power estimates were obtained with a cortically-constrained minimum norm method applied to total complex power spectra within an aMEG approach (Kovacevic et al., 2012, Marinkovic et al., 2012b). This model requires no a priori assumptions regarding the number or locations of the sources and it produces inverse estimates based on all sensor channels and without user interventions. Within this linear model, activity estimates are obtained for each cortical dipole and for each time-point, resulting in continuous spatio-temporal maps (i.e. movies) of brain activity (Dale et al., 2000; Kovacevic et al., 2012; Marinkovic et al., 2012b). The data collected from the empty magnetically-shielded room were wide band-passed (3 to 40 Hz) and used for estimation of noise covariance to prevent biasing the inverse solution against spontaneous brain oscillations. For each participant, average maps of estimated total event-related theta source power were computed as relative change from the prestimulus period, −300 to 0 ms. Individual source power estimates were averaged by aligning their sulcal-gyral patterns at each time point (Dale et al., 2000). Region-of-interest (ROI) analysis was conducted to further examine possible interactions of the factors of beverage and task condition on changes in theta power. ROIs were selected based on the overall group average across all participants, task, and beverage conditions in a manner blind to each participant's individual activation. ROIs are created to represent groups of dipoles along the cortical surface with most notable source power at a certain threshold. This approach is rather conservative, as it does not allow for idiosyncrasies in terms of spatial distribution or latency between participants. Consequently, only those activity differences that overlap highly in both time and cortical space across participants for a particular contrast have a chance of being significant. Within each ROI, for each participant and condition, the estimates are calculated by averaging across all cortical points comprised in the ROI and are presented as percent change from baseline. More specifically, ROIs included bilateral dorsal and rostral anterior cingulate cortex (dACC and rACC, respectively), pre-/SMA, inferior frontal cortex (IFC), and hand sensorimotor region (sMOT) in the central sulcus, as well as the right lateral temporal cortex (LTC), and anterior insula (INS). The same set of group-based ROIs was used for all participants in a manner blind to their individual activations.

To investigate spatio-temporal stages of inhibitory control, correct Go (response execution) and correct NoGo (response inhibition) trials were epoched based on stimulus onset. Artifact-free correct Go trials were selected at random to match the number of included NoGo trials across the beverage conditions for each participant. Event-related theta to correct Go and NoGo inhibition trials was examined within the 270 to 420 and 200 to 350 ms time window respectively.

Response-locked epoching with respect to button pressing was used to examine NoGo errors and correct Go responses (Kovacevic et al., 2012). Twelve participants made a sufficient number of errors (20 or more) and were included in the error and post-error analysis streams. The early error-evoked theta peak was examined within 50 to 200 ms post-response, and the later one within 300 to 400 ms time interval. Ordinal features of post-error adjustments were investigated using first five stimulus-locked correct Go trials that followed error or correct NoGo trials within 200 to 450 ms time window. One participant was excluded from post-error analysis as an outlier. Because these findings are based on a small sample, they should be considered preliminary and explorative and would need to be replicated in future studies.

Behavioral and event-related theta variables were analyzed with fixed effects repeated measures 2×2 ANOVAs with factors of Beverage (alcohol, placebo) and Condition (Go, NoGo/Error). Correlation coefficients were calculated between behavioral and

neural indices of inhibitory control including error processing, and dispositional impulsivity/risk-taking as probed with psychoticism (P-scale) measured with EPQ-R (Eysenck et al., 1985). In addition, correlations were computed between the theta to NoGo errors in the dACC and subsequent Go trials. A false discovery rate method with FDR = 0.1 was used to control for multiple correlations (Hochberg & Benjamini, 1990).

To assess trial-to-trial modulations following erroneous NoGo responses, a multilevel generalized linear model (GLM) was fit to the data (matlab: `fitglme`) where the response variable right dACC theta (continuous) is predicted by fixed-effects variables beverage (categorical) and post-error trial position (continuous), which are both nested in the random effects variable subject (categorical) as well as an intercept term. An identical model was fit to the response variable behavioral accuracy (continuous) on post-error trials.

RESULTS

Behavioral results

Task performance

Participants made a substantial number of commission errors by failing to inhibit responses on NoGo trials, while their accuracy, or the rate of response on Go trials was nearly perfect (Figure 2A). A Beverage by Condition interaction, F (1, 15) = 19.2, $p < 0.01$, revealed that alcohol selectively decreased only NoGo accuracy, F (1, 15) = 15.1, $p < 0.01$, which equaled 73.86 ± 13.5% (mean ± SD) under placebo and 62.05 ± 17.1% under alcohol. Go accuracy was unaffected by alcohol (97.5%), F (1, 15) = 0.5, $p > 0.05$. As shown in Figure 2B, there were no effects of beverage on RTs to Go (385.9 ± 67.2 ms), F (1, 15) = 0.62, $p = 0.44$, or erroneous NoGo trials (399.4 ± 77.1 ms), F(1, 15) = 0.54, $p = 0.47$. Participants with higher impulsivity were less successful at inhibiting responses to NoGo stimuli under placebo. More specifically, accuracy on NoGo trials correlated negatively with EPQ-P scores, $r = -0.53$, $p = 0.03$, reflecting the expected association between dispositional risk-taking traits and behavioral inhibitory control.

Post-experimental questionnaire and mood ratings

Participants rated the task as being moderately difficult, but comparably so under alcohol (3.3 ± 1.0) and placebo (3.5 ± 1.4, $\chi^2 = 0.4$, $p > 0.1$). On the scale from 1 (not at all) to 5 (very much), participants reported feeling moderately intoxicated under alcohol (2.6 ± 0.8), but not at all under placebo (1.1 ± 0.3, $\chi^2 = 14.0$, $p < 0.0005$). As expected, participants felt more stimulated during the ascending phase under alcohol compared with placebo, F (1, 15) = 4.66, $p < 0.05$ relative to baseline. Subjective ratings of sedation were higher at the end of the experiment overall, F = 8.80, $p < 0.01$, but were not affected by beverage. These results are consistent with previous reports (Kovacevic et al., 2012; Marinkovic et al., 2012a).

MEG spatio-temporal estimates

Lateralized activity during successful response execution (Go) and inhibition (NoGo)

Response execution and inhibition were characterized by a strongly lateralized pattern of event-related theta power activity (Figure 3). While Go trials activated primarily sensorimotor areas in the left hemisphere, successful inhibition on NoGo trials was reflected in the right fronto-temporal theta activity. As expected, correct response execution (Go trials) elicited much greater theta power than response withholding (NoGo) in the left sMOT and SMA contralateral to the responding hand (Table 1A; Figure 3A). Alcohol intoxication attenuated theta power in the left sMOT, with a greater effect on Go trials. Alcohol also reduced theta to Go trials in the left IFC. However, it had no effect on the left SMA which was sensitive only to task demands.

In contrast, successful response inhibition on NoGo trials elicited greater theta power in a strongly right lateralized network (Table 1A; Figure 3B). NoGo theta power was increased relative to Go trials in the right IFC, LTC, and the right ACC. Alcohol specifically reduced NoGo theta in the right IFC, LTC, SMA, and ACC, but it did not reliably affect theta on Go trials in these areas, consistent with its selective impact on top-down inhibitory control (Kovacevic et al., 2012; Marinkovic et al., 2012b; Marinkovic et al., 2019). More impulsive

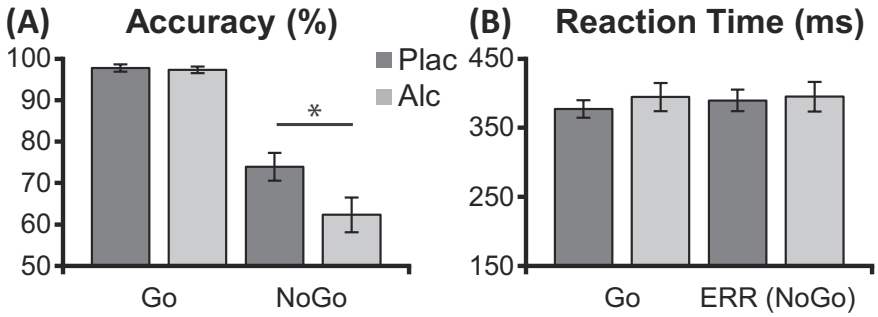

FIGURE 2 Performance measures (means ± standard errors) for: (A) Go and NoGo accuracy, (B) reaction times to correct Go and erroneous NoGo responses for both beverage conditions. Alcohol increased the number of NoGo errors (*$p < 0.05$), but did not affect RTs

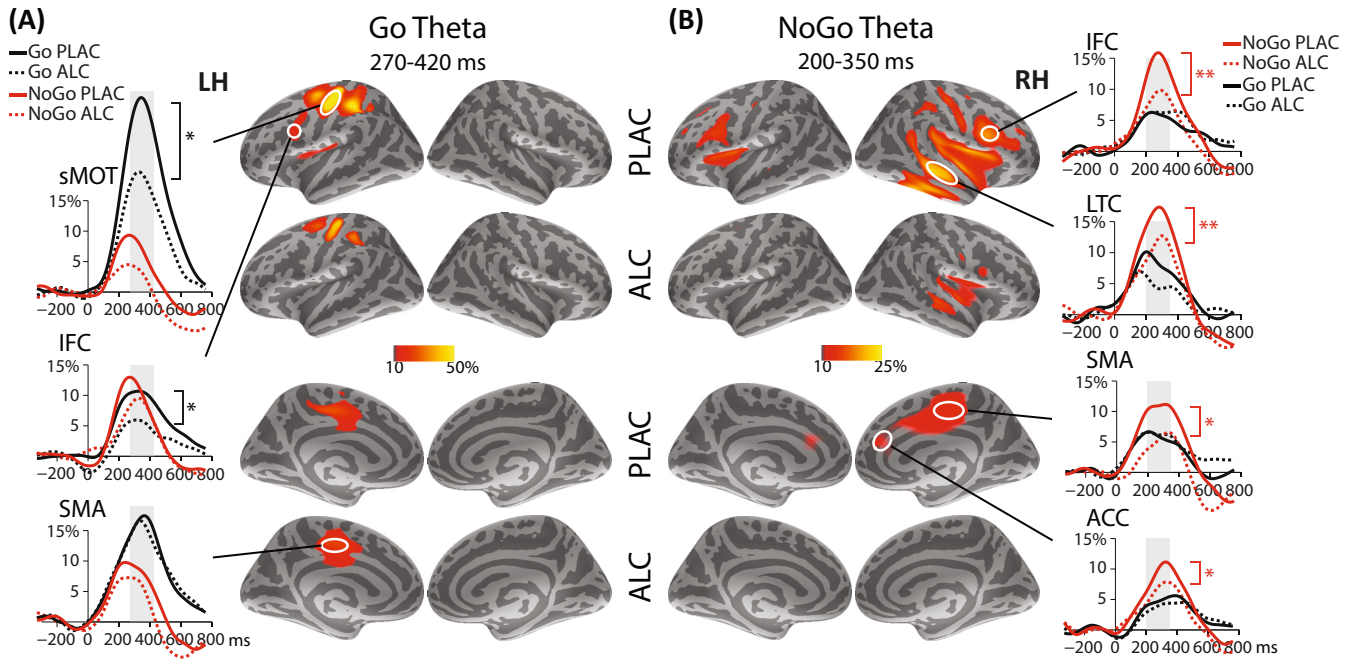

FIGURE 3 Group-average maps of event-related theta source power estimates for successful response execution (Go) and inhibition (NoGo) are shown on an inflated template cortex for both hemispheres laterally (top two rows) and medially (bottom two rows), for both alcohol and placebo sessions. Time-courses of estimated activity are shown for the most prominent loci. (A) Successful response execution on Go trials elicited a much larger event-related theta power increase in the left sensorimotor (sMOT) cortex and the SMA than response withholding on NoGo trials. Alcohol attenuated Go theta in the left sMOT and the left IFC, $^{*}p < 0.05$. (B) Successful response inhibition on NoGo trials elicited event-related theta power predominantly in the right frontal and temporal cortices. Alcohol reduced theta power selectively on NoGo trials in the right IFC, LTC, SMA, and the ACC, $^{*}p < 0.05$, $^{**}p < 0.01$

participants showed decreased theta on NoGo trials. In particular, NoGo theta was negatively correlated with the P-scale (EPQ-R) scores in the right ACC ($r = -0.73$, $p = 0.001$), and in the right IFC ($r = -0.58$, $p = 0.02$).

Inhibition failures: NoGo errors

To examine the activity pattern associated with making an error, we used response-locked theta estimates that were aligned to erroneous responses (NoGo error) in comparison with correct (Go) button presses (Table 1B; Figure 4), under placebo and alcohol. Failing to inhibit responses on NoGo trials (errors of commission), elicited an increase in theta power peaking at ~110 ms post-response in the right INS and bilateral dACC, compared with correct Go responses. The NoGo theta in dACC correlated negatively with RTs to Errors ($r = -0.62$, $p = 0.03$), as greater theta was associated with shorter, presumably more rash erroneous responses. Alcohol attenuated NoGo error-related theta in the right INS, and marginally so in the right dACC at ~110 ms (Table 1B).

This activity pattern changed dynamically as the error-related peak (~110 ms) was followed by theta increase to errors in the bilateral rACC in the 300 to 400 ms time window under placebo (Figure 4B). This delayed engagement of the rostral ACC by errors correlated negatively with risk taking/ impulsivity as measured with the P-scale (EPQ-R; $r = -0.74$, $p < 0.01$), but not with error RTs ($r = 0.07$, $p = 0.82$). The activity anteriorization was attenuated by alcohol bilaterally in the rACC.

Post-error adjustments: engagement of cognitive control

Behavioral and event-related theta indices on Go trials following errors were compared with the Go trials after correct NoGo inhibitions. As shown in Figure 5A, a drop in performance accuracy after NoGo errors was especially evident under placebo, as participants missed more of the first Go trials after a commission error than after a successful inhibition, F (1, 10) = 9.0, $p < 0.05$. In addition, they showed PES, that is, their responses were slower to the first Go after a commission error than after a successful inhibition under placebo, F (1, 10) = 6.9, $p < 0.05$ and marginally so under alcohol, F (1, 10) = 3.6, $p < 0.1$.

Next, we explored whether error-related theta power in the dACC could predict theta power on the first subsequent Go trial (Figure 5B), possibly signifying engagement of cognitive control and successful adjustments on post-error trials. Only under placebo did error-related theta in the right dACC correlate reliably with theta on a subsequent Go trial in the left lateral (sMOT $r = 0.82$, $p = 0.002$) and medial motor cortices (SMA $r = 0.76$, $p < 0.007$), with FDR adjustment.

Finally, we explored trial-to-trial modulations following commission errors (Figure 5C). The right dACC was the only region that showed post-error trial-to-trial modulations on Go trials, which was

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TABLE 1 ANOVA summary

	Condition	Beverage	Cond × Bev	Plac NoGo vs Go	Alc NoGo vs Go	NoGo Plac vs Alc	Go Plac vs Alc
Overall activity (Figure 3)							
270 to 420 ms							
sMOT-lh	33.81***	5.92*	3.4	24.96***	26.67***	4.13	5.35*
IFC-lh	0.47	2.64	3.07†	0.01	1.46	0.43	7.1*
SMA-lh	35.45***	0.76	0.4	12.70**	42.06***	1.45	0.15
200 to 350 ms							
IFC-rh	14.69**	4.4†	5.68*	18.75***	2.01	10.52**	0.03
MTC-rh	11.26**	10.87**	0.38	10.86**	7.89*	14.61**	3.79†
SMA-rh	3.12†	1.36	7.59*	11.77**	0.28	5.06*	0.03
ACC-rh	6.64*	3.3†	0.843	4.54*	5.26*	6.22*	0.27
	Condition	**Beverage**	**Cond × Bev**	**Plac Err vs Go**	**Alc Err vs Go**	**Errors Plac vs Alc**	**Go Plac vs Alc**
Errors vs Go (Figure 4)							
50 to 200 ms							
INS-rh	6.53*	10.53**	3.5†	8.25*	1.5	8.97*	1.4
dACC-lh	12.50**	0.19	0.48	14.63**	8.35*	0.44	0.02
dACC-rh	22.77***	5.233*	0.5	11.26**	9.2*	3.71†	0.88
300 to 400 ms							
rACC-lh	7.04*	2.21	7.76*	22.96***	0.07	11.41**	0.77
rACC-rh	5.47*	1.02	4.99*	7.54*	0.97	10.76**	0.63

Note. Summary of ANOVAs of event-related theta power reflecting a) the overall activity (Figure 3) and b) error-related activity (Figure 4) for different ROIs. Included are the results for main effects and interactions of the factors of Condition (NoGo or Error and Go) and Beverage (alcohol and placebo). Lh, left hemisphere; rh, right hemisphere. ROIs, sMOT, sensorimotor cortex; IFC, inferior frontal cortex; SMA, supplementary motor area; LTC, lateral temporal cortex; INS, insula; ACC, anterior cingulate cortex with d (dorsal) and r (rostral) subdivisions. Panel (a) shows *F*-values with 1, 15 degrees of freedom and (b) shows *F* (1, 11). †$p < 0.1$, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

evident only under placebo. Mixed-effects GLMs were constructed to analyze the variance of post-error trial-to-trial event-related theta power and behavioral accuracy following NoGo commission errors. The beverage × trial position interaction on post-error theta was marginally significant, F (1, 84) = 3.69 $p < 0.06$, while neither beverage nor trial position had significant main effects. These results were closely echoed in post-error behavioral accuracy, on which the effects of beverage condition and post-error trial position interacted, F (1, 84) = 8.16, $p < 0.006$, but the main effects did not reach significance. The beverage × trial position interaction was explored with post-hoc mixed-effects GLMs for each beverage condition and is driven by effects of trial position on theta, F (1, 42) = 2.56, $p = 0.11$, and accuracy F (1, 42) = 6.18, $p < 0.02$ in the placebo condition, whereas these effects are absent in the alcohol condition, with F(1, 42) = 1.12, $p = 0.30$ and F(1, 42) = 0.16, $p = 0.69$ for theta and accuracy, respectively. Thus, alcohol intoxication dysregulated these post-error adjustments on Go trials after errors.

DISCUSSION

This study used a multimodal approach to examine the spatiotemporal features of event-related theta power characterizing different aspects of processing engaged by a Go/NoGo task in the context of alcohol challenge. We analyzed the neural underpinnings of successful response inhibition, error-related activity, and trial-to-trial dynamics of post-error changes. Correct task performance was subserved by lateralized theta activity. Go trials elicited left-dominant theta in the lateral and medial motor areas, which is expected given that responses were made with the right index finger. In contrast, successful response withholding on NoGo trials resulted in greater theta power in right-lateralized fronto-temporal areas (Figure 3). Error commission was first accompanied with an immediate increase in theta power in the bilateral dACC and the right INS at ~110 ms (Figure 4). The dominant activity focus then shifted anteriorly to the rACC (300 to 400 ms), which may be indicative of error awareness and an unpleasant "oh no!" engagement of the limbic circuitry. Lower accuracy and PES were observed on the first post-error Go trial. In addition, NoGo error-related theta estimated to the dACC correlated with post-error Go theta in the motor cortical areas, which is indicative of adjustments in motor planning. A striking finding is the multi-trial dynamics of the post-error modulation of theta estimated to the dACC. It increased across trials, tracking improvement in accuracy on the successive post-error Go trials, which may reflect gradual enhancement of cognitive control engagement on Go trials after a NoGo commission error.

Acute alcohol affected behavioral and neural indices measured during successful Go/NoGo response execution and inhibition, error

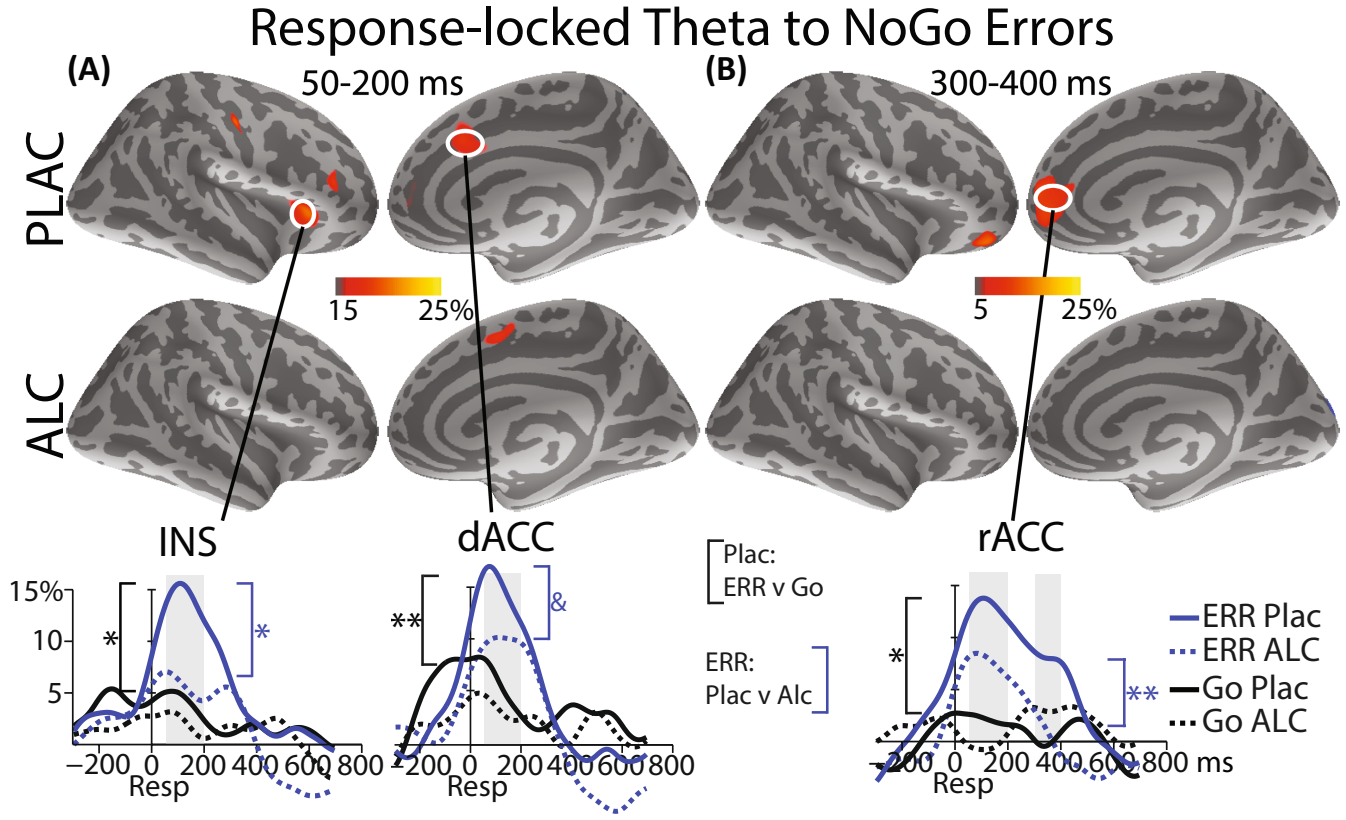

FIGURE 4 Group-average maps of response-locked event-related theta source power estimates in the right hemisphere in the 50 to 200 ms (a) and 300 to 400 ms (b) time windows following erroneous button presses on NoGo Err trials and correct Go responses. Time-courses of the activity estimated to the insula (INS), dorsal ACC (dACC) and rostral ACC (rACC) are shown in the lower panel. Under placebo, NoGo errors elicit greater theta immediately after an error, followed by another theta peak in the rACC ~250 ms later. Alcohol attenuated error-related theta in the INS and rACC. $^{\&}p = 0.08$, $^{*}p < 0.05$, $^{**}p < 0.01$

processing, and post-error adjustments. When intoxicated, participants made more commission errors on NoGo trials (Figure 2), confirming that alcohol selectively impairs inhibitory control (Loeber & Duka, 2009), which has been shown to predict ad lib consumption and alcohol-related problems (Corbin et al., 2020; Field et al., 2010; Weafer & Fillmore, 2008). Indeed, alcohol attenuated NoGo theta predominantly in the right frontal cortices (Figure 3), consistent with its deleterious effects on top-down control (Anderson et al., 2011; Bartholow et al., 2003; Curtin & Fairchild, 2003; Kovacevic et al., 2012; Marinkovic et al., 2012a; Marinkovic et al., 2012b; Marinkovic et al., 2013; Rosen et al., 2016). During error processing and post-error adjustments, the most pronounced alcohol effects were evident in the ACC, as post-error recovery of cognitive control was dysregulated by alcohol (Figures 4 and 5). These results confirm extensive evidence indicating that a moderately low alcohol dose primarily affects decision making, the network subserving cognitive control (Bailey et al., 2014; Bartholow et al., 2012; Cofresi & Bartholow, 2020; Field et al., 2010; Holroyd & Yeung, 2003; Marinkovic et al., 2012a; Marinkovic et al., 2013; Ridderinkhof et al., 2002). Over time, alcohol-induced disinhibition may give rise to compulsive drinking and the development of alcohol use disorder (Field et al., 2010; Fillmore, 2003).

Inhibitory control is subserved by a right-dominant network

Numerous neuroimaging studies have shown that inhibitory control is associated with right-dominant frontal activity encompassing the right dorsolateral and IFC, INS, preSMA, and STC (Aron et al., 2014; Criaud & Boulinguez, 2013; Garavan et al., 2002). However, fMRI lacks the temporal precision needed to reveal how these contributions to inhibitory control unfold in time. In the present study, we used cortical surface-constrained distributed source modeling to analyze MEG signal in time-frequency domain in theta band. Our results are broadly consistent with neuroimaging evidence, as successful response inhibition on NoGo trials was accompanied with increased theta power in a right lateralized network, with major contributions from the right IFC, LTC, SMA, preSMA, and ACC. Theta power increased concurrently across these areas and peaked at ~300 ms after stimulus onset. Prominent accounts have proposed that cognitive control emerges from a dynamic interplay between the medial and lateral prefrontal cortices (Botvinick, 2007). On that view, the ACC/preSMA is a central hub for cognitive control that monitors for conflicting representations and integrates the present behavior with strategic planning and

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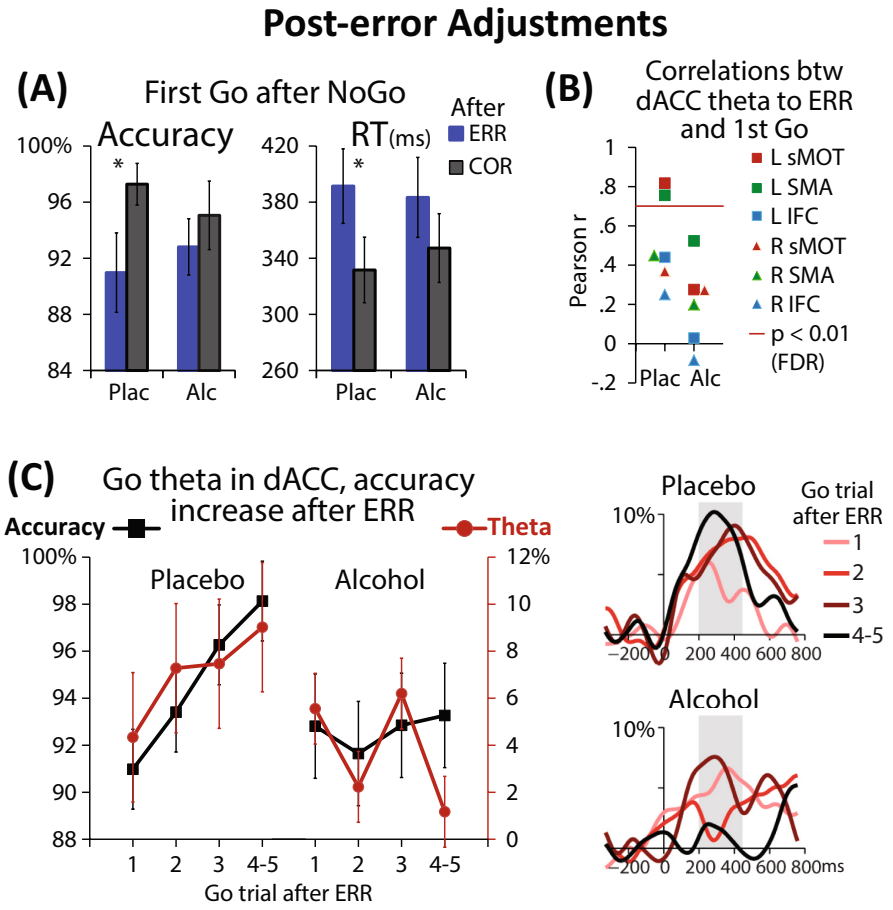

FIGURE 5 (A) Accuracy and RTs on the first Go trial following NoGo errors and correct NoGo trials. Reduced accuracy and RT slowing was observed on the first post-error Go trials, $^{*}p < 0.05$. (B) Theta elicited by NoGo errors in the right dorsal ACC predicts theta power on the subsequent Go trial in the left lateral (sMOT) and medial (SMA) motor cortices. (C) On Go trials following NoGo errors, theta increase in the right dorsal ACC (200 to 450 ms) tracks trial-to-trial improvement in accuracy under placebo. In contrast, the post-error adjustments of accuracy and theta power were dysregulated by alcohol. Time-courses of theta estimated to the dACC on post-error Go trials are shown in the right panel

motivational constrains, while the IFC implements the necessary adjustments (Heilbronner & Hayden, 2016; Kolling et al., 2016; Sheth et al., 2012). Indeed, we have recently shown that the ACC and the IFC interact synchronously in real time in theta frequency band in a manner reflecting engagement of cognitive control (Marinkovic et al., 2019), which is consistent with other evidence indicating that theta underlies long-range neural interactions with relevance to top-down control (Cavanagh & Frank, 2014; Cohen, 2016; Marinkovic et al., 2019; Wang et al., 2005). Event-related theta power reflects cognitive conflict and decision making, and it scales up with task difficulty (Rosen et al., 2016). Human intracranial and EEG source modeling studies have confirmed theta generators in the ACC and the surrounding medial prefrontal cortex during cognitive control tasks (Cavanagh & Frank, 2014; Wang et al., 2005). In addition, other medial frontal areas including the SMA and preSMA play a key role in selection, preparation, and the execution of motor responses (Nachev et al., 2008). The lateral IFC is also strongly activated by tasks probing inhibitory control (Aron et al., 2014) which relies on both, attentional and inhibitory components due to salience, oddball characteristics, and task demands imposed by NoGo stimuli. Nonetheless, the view that the right IFC exerts primarily inhibitory effects on motor function (Aron et al., 2014) is supported by our recent study which manipulated attentional and inhibitory task aspects (Happer et al., 2021). In the current study, the right LTC also showed a strong response to NoGo trials, reflecting its sensitivity to stimulus salience as part of the ventral attentional system (Halgren et al., 2011; Happer et al., 2021).

Impulsivity and risk taking, as measured with EPQ-R (Eysenck et al., 1985), correlated negatively with NoGo accuracy and with NoGo theta power estimated to the ACC, which is consistent with similar findings in individuals with AUD (Kamarajan et al., 2012). Here, we have shown that alcohol selectively reduced theta during inhibitory control (NoGo trials), which confirms extensive prior evidence of alcohol-induced impairments of top-down executive regulation in social drinkers (Anderson et al., 2011; Bartholow et al., 2003; Curtin & Fairchild, 2003; Kovacevic et al., 2012; Marinkovic et al., 2012a; Marinkovic et al., 2013; Rosen et al., 2016), with potential relevance to the development of compulsive drinking (Field et al., 2010, Fillmore, 2003).

Inhibition errors elicit theta first in the dorsal, then rACC, indicative of cognitive-affective interplay

Commission errors elicited an increase in theta power in the bilateral dACC and the right anterior INS (Figure 4). This is consistent with EEG studies using dipole source localization methods that estimated ERN generator to the medial frontal cortex (Taylor et al., 2007; van Veen & Carter, 2006). It also aligns with extensive fMRI evidence confirming the ACC involvement in error processing (Ridderinkhof et al., 2004). Theta power to errors increased concurrently in the right INS, in agreement with studies reporting fronto-striatal contributions to error-related activity (Ullsperger et al., 2014). Critically, theta power increase in the dACC that occurred ~100 ms after an error (Figure 4A), was followed by activity in the rostral ACC during a subsequent (~350 ms) stage of error processing (Figure 4B). Studies using scalp ERN measures have similarly reported that an estimated rACC generator becomes active to errors at ~300 ms, following the ERN (Van Veen & Carter, 2002).

It has been well established that negative affect is an important component of cognitive control processes engaged by errors in the service of adaptive behavior optimization and emotion regulation (Dignath et al., 2020). Our finding that, after an error, theta in the rACC follows the dACC, is consistent with an affective engagement of the limbic circuitry. Indeed, their timing and spatial attributes are aligned remarkably well with confirmatory intracranial EEG (iEEG) evidence of delayed, error-specific activity in the rACC (Bonini et al., 2014). Furthermore, iEEG recordings show that the amygdala mediates error monitoring during a Go/NoGo task, as event-related theta generated in the amygdala is coupled with theta in the pre-SMA with a delay of ~300 ms after committing an error (Pourtois et al., 2010). Because errors are aversive and occur unexpectedly, they elicit an "oh, no!" orienting response (Wessel, 2018a). Activity in the rACC is associated with error-related arousal, particularly when errors signify punishment in the form of monetary loss (Taylor et al., 2007). Given an essential role of the rACC in the processing of self-relevant information, this delayed activity could reflect awareness of an error, or an error-elicited negative emotional state (Hughes & Yeung, 2011; Van Veen & Carter, 2002). Even though the distinction between cognition and emotion is becoming increasingly blurred, neuroimaging evidence indicates that the dorsal and rostral ACC perform complementary cognitive and affective or motivational functions in response to errors (Steele & Lawrie, 2004). While the dACC is a key hub of cognitive control as it monitors for conflict and mediates post-error adjustments (Ridderinkhof et al., 2004; Ullsperger et al., 2014; Wessel, 2018a), the rACC has been implicated in guiding behavior based on the evaluation of the emotional and reward-related input, and its connections with limbic structures (Tang et al., 2019; Taylor et al., 2007; Ullsperger et al., 2014).

Taken together, our results are broadly aligned with an affective-signaling hypothesis, which proposes that cognitive control relies on emotional input to effectuate adaptive changes aiming to reduce conflict (Dignath et al., 2020). On this view, errors are accompanied with an interplay of cognitive-affective contributions represented in a caudo-rostral medial prefrontal sequential activity gradient. Our results suggest that the dACC may contribute to the early error detection, followed by rACC involvement in the later, affective stage of error processing, possibly reflecting the "oh, no!" moment. This integrated processing sequence is greatly attenuated by alcohol intoxication, confirming previous reports of alcohol-induced ERN (Bailey et al., 2014; Bartholow et al., 2012; Cofresi & Bartholow, 2020; Holroyd & Yeung, 2003; Ridderinkhof et al., 2002), and dysregulation of neural synchrony (Marinkovic et al., 2019). Alcohol may exert attenuating effects on both, error detection, and the subjective experience of error commission. By reducing theta power in the principal hubs of cognitive control, alcohol intoxication may make it difficult to engage performance monitoring functions and could blunt the negative affect that accompanies errors, which, in turn, could undermine behavioral adjustments and impair the ability to refrain from drinking. In a series of alcohol challenge studies, Bartholow and colleagues have used ERN, behavioral, and complementary peripheral measures of negative affect, to examine the affective aspects of error processing and post-error adjustments (Bailey et al., 2014, Bartholow et al., 2012, Cofresi & Bartholow, 2020). Their studies provide converging evidence supporting the idea that alcohol blunts error-induced negative affect, which mediates post-error adjustments (Bartholow et al., 2012).

In the present study, the delayed rACC theta power was negatively associated with P-scores, which is indicative of impulsivity and risk taking, confirming previous findings (Hall et al., 2007). Disinhibition and propensity for risk taking have been linked to the vulnerability for developing alcohol or drug use disorders (Field et al., 2010; Fillmore, 2003; Weafer et al., 2014). Furthermore, higher impulsivity is related to lower frontal theta in a gambling task in individuals with AUD (Kamarajan et al., 2012). Alcohol-induced impairment of inhibitory control, as indicated by premature motor preparation, is associated with impulsivity (Marinkovic et al., 2000). Therefore, our results confirm previous suggestions that alcohol-related deficits in action monitoring may predispose individuals to engaging in risky behavior such as excessive drinking.

Post-error adjustments: parallel increase of theta and response accuracy across trials

An aspect of error-related processing that is most relevant to behavior optimization is what happens *after* an error has been committed. PES is taken to signify enhanced controlled processing in the service of minimizing error likelihood (Danielmeier & Ullsperger, 2011). It also reflects attentional capture after an error (Happer et al., 2021; Wessel, 2018a), which is especially relevant to the current Go/NoGo task version. Go stimuli were presented in rapid succession (1200 ± 100 ms) on the majority of trials (80%), resulting in motor readiness, as responses were pre-initiated on each trial and had to be occasionally suppressed. Because the NoGo errors are rare, unexpected, and highly salient, these trials

elicit attentional orienting which results in momentary motor "braking" or even stopping (Wessel, 2018a). In a recent report, we have confirmed that attentional capture acts as a "circuit breaker" as it disrupts the ongoing motor preparation, resulting in lower Go accuracy (Happer et al., 2021). In the present study, the first post-error Go trial followed this pattern as it was characterized by decreased accuracy and slower RTs under placebo (Figure 5A). In contrast, these effects were absent during alcohol intoxication, confirming its deleterious impact on cognitive control (Bartholow et al., 2012, Holroyd & Yeung, 2003; Marinkovic et al., 2012a; Marinkovic et al., 2013; Ridderinkhof et al., 2002; van Veen & Carter, 2006).

Our data provide further insight into theta dynamics of post-error tuning, revealing how neural adjustments are implemented for the purpose of behavioral optimization sequentially across trials. More specifically, theta to errors in the right dACC correlated positively with theta in the medial and lateral motor cortices on the first post-error Go trial (Figure 5B), supporting the view that the dACC may engage cognitive control of the relevant post-error downstream areas on subsequent trials (Danielmeier & Ullsperger, 2011). In agreement with adaptive theories of error processing, the dACC has been strongly implicated in supporting contextual representation and strategic planning by flexibly accounting for future benefits (Heilbronner & Hayden, 2016; Sheth et al., 2012).

To examine the underpinnings of sequential cognitive control adjustments, we extended the analysis to several post-error Go trials. Interestingly, under placebo, the dACC exhibited trial-to-trial increase in theta power on the trials following commission errors, which closely followed improvements in accuracy (Figure 5C). This is indicative of cognitive control engagement in the service of post-error adaptive response optimization across trials. In contrast, no such increase is observed under alcohol, confirming its deleterious effects on post-error adaptation mechanisms, possibly by disrupting long-range cortical synchrony (Marinkovic et al., 2019), but see (Bailey et al., 2014). The gradual increase of post-error power in the dACC may reflect anticipation of the rising probability of NoGo trials and, consequently, errors. This pattern is consistent with a known role of the dACC in updating predictions of cognitive demand, and in correcting the inappropriate activation to avoid making an error (Heilbronner & Hayden, 2016, Sheth et al., 2012). The dACC was the only brain region that showed these modulations, suggesting that post-error adjustments are directly related to modulations in the dACC activity. Although studies focusing on sequential post-error changes across time are scarce, this type of evidence can provide insight into the dynamics of behavioral adjustments aimed at preventing errors.

Limitations of the study

Results of the present study should be interpreted with due consideration of their limitations. The sample size was small, which necessarily limits the generalizability of the findings. Even though this concern is somewhat mitigated by the within-subjects design as it controls for idiosyncrasies in neuroanatomy and neurophysiology, these results should be replicated in future studies. This is particularly relevant to the post-error responses which are considered to be preliminary and explorative. Furthermore, analyses of the oscillatory activity in other frequency bands such as beta and alpha, would provide additional, and more complete insight into the neural underpinnings of the effects of alcohol on inhibitory control.

In sum, this study confirms the importance of frontal theta oscillations for successful inhibitory control, as well as for error-related and post-error processing. The results support the functional and temporal dissociation along the dorso-rostral axis of the ACC, with the dACC contributing to the early error detection, followed by an affective "oh, no!" response of the rACC. Critically, post-error theta increase tracked improvements in accuracy across trials under placebo. By compromising top-down cognitive control, alcohol intoxication may contribute to self-control impairments and the inability to refrain from drinking.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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