Journal of Visualized Experiments

Disruption of frontal lobe neural synchrony by alcohol intoxication

--Manuscript Draft--

Article Type:	Invited Methods Article - JoVE Produced Video
Manuscript Number:	JoVE58839R1
Full Title:	Disruption of frontal lobe neural synchrony by alcohol intoxication
Keywords:	Neuroscience; brain; cognitive control; Magnetoencephalography; theta oscillations; phase-locking; neural synchrony; Alcohol; Stroop task; multimodal imaging
Corresponding Author:	Ksenija Marinkovic San Diego State University San Diego, CA UNITED STATES
Corresponding Author's Institution:	San Diego State University
Corresponding Author E-Mail:	kmarinkovic@sdsu.edu
Order of Authors:	Ksenija Marinkovic
	Lauren E Beaton
	Burke Q Rosen
	Joseph P Happer
	Laura C Wagner
Additional Information:	
Question	**Response**
Please indicate whether this article will be Standard Access or Open Access.	Standard Access (US$2,400)
Please indicate the **city, state/province, and country** where this article will be **filmed**. Please do not use abbreviations.	San Diego, California, United States of America

Cover Letter

Ksenija Marinković, Ph.D.

Associate Professor
Psychology Department
San Diego State University
Spatio-Temporal
Brain Imaging Laboratory
MC-1879
6505 Alvarado Rd. Suite 202
San Diego, CA 92120
tel. (619)594-1510
email: kmarinkovic@mail.sdsu.edu

Center for Clinical
and Cognitive Neuroscience
Core faculty
San Diego State University

http://stbil.sdsu.edu/index.html

Adjunct Associate Professor
Department of Radiology
University of California, San Diego

July 27, 2018

To the Science Editor,
Journal of Visual Experiments

Dear Dr. Myers,

Please consider for publication the enclosed manuscript entitled "Turning off the executive: Disruption of frontal lobe neural synchrony by alcohol intoxication" by Marinkovic, Beaton, Rosen, Happer, and Wagner.

Our study combined MEG source modeling and structural MRI in response to Stroop interference to examine the cortical areas involved in cognitive control, to characterize the temporal sequence of their activation, and to quantify the oscillatory dynamics of their neural interactions in real time. Because MEG signal reflects synaptic currents directly, it has excellent temporal resolution and can resolve successive spatio-temporal stages of processing with high precision. For the same reason, it is suitable for pharmacological manipulations unlike fMRI, which is susceptible to vascular confounds. In the present study, young, healthy individuals were given a moderate alcohol dose in a within-subject design. The results indicate that acute intoxication attenuated theta power to Stroop conflict and dysregulated co-oscillations between the medial and lateral prefrontal areas known to be the hubs of cognitive control. This method can provide insight into real-time interactions during cognitive processing and can be used across a variety of tasks and manipulations.

Please note that the study was conducted in accord with APA standards for ethical treatment of subjects and was approved by the institutional review board.

All co-authors have approved the submitted manuscript.

There were no conflicts of interest regarding the research reported in this manuscript.

On behalf of all co-authors, I thank you for your consideration.

Sincerely,

Ksenija Marinković, Ph.D.

TITLE:

Disruption of Frontal Lobe Neural Synchrony by Alcohol Intoxication

AUTHORS AND AFFILIATIONS:

Ksenija Marinkovic[1,2], Lauren E. Beaton[1], Burke Q. Rosen[3,1], Joseph P. Happer[4], Laura C. Wagner[1]

[1]Department of Psychology, San Diego State University, San Diego, CA, USA
[2]Department of Radiology, University of California San Diego, San Diego, CA, USA
[3]Department of Neurosciences, University of California San Diego, San Diego, CA, USA
[4]San Diego State University/UC San Diego Joint Doctoral Program in Clinical Psychology, San Diego, CA, USA

Corresponding Author:

Ksenija Marinkovic (kmarinkovic@sdsu.edu)

Email Addresses of Co-authors:

Lauren E. Beaton (lbeaton@sdsu.edu)
Burke Q. Rosen (bqrosen@gmail.com)
Joseph P. Happer (jhapper@sdsu.edu)
Laura C. Wagner (lwagner@sdsu.edu)

KEYWORDS:

Neuroscience, brain, cognitive control, magnetoencephalography, theta oscillations, phase-locking, neural synchrony, alcohol, Stroop task, multimodal imaging

SUMMARY:

This experiment uses an anatomically-constrained magnetoencephalography (aMEG) method to examine brain oscillatory dynamics and long-range functional synchrony during engagement of cognitive control as a function of acute alcohol intoxication.

ABSTRACT:

Decision making relies on dynamic interactions of distributed, primarily frontal brain regions. Extensive evidence from functional magnetic resonance imaging (fMRI) studies indicates that the anterior cingulate (ACC) and the lateral prefrontal cortices (latPFC) are essential nodes subserving cognitive control. However, because of its limited temporal resolution, fMRI cannot accurately reflect the timing and nature of their presumed interplay. The present study combines distributed source modeling of the temporally precise magnetoencephalography (MEG) signal with structural MRI in the form of “brain movies” to: (1) estimate the cortical areas involved in cognitive control (“where”), (2) characterize their temporal sequence (“when”), and (3) quantify the oscillatory dynamics of their neural interactions in real time. Stroop interference was associated with greater event-related theta (4 - 7 Hz) power in the ACC during conflict detection followed by sustained sensitivity to cognitive demands in the ACC and latPFC during integration and response preparation. A phase-locking analysis revealed co-

oscillatory interactions between these areas indicating their increased neural synchrony in theta band during conflict-inducing incongruous trials. These results confirm that theta oscillations are fundamental to long-range synchronization needed for integrating top-down influences during cognitive control. MEG reflects neural activity directly, which makes it suitable for pharmacological manipulations in contrast to fMRI that is sensitive to vasoactive confounds. In the present study, healthy social drinkers were given a moderate alcohol dose and placebo in a within-subject design. Acute intoxication attenuated theta power to Stroop conflict and dysregulated co-oscillations between the ACC and latPFC, confirming that alcohol is detrimental to neural synchrony subserving cognitive control. It interferes with goal-directed behavior that may result in deficient self-control, contributing to compulsive drinking. In sum, this method can provide insight into real-time interactions during cognitive processing and can characterize the selective sensitivity to pharmacological challenge across relevant neural networks.

INTRODUCTION:

The overall goal of this study is to examine the effects of acute alcohol intoxication on spatio-temporal changes in the brain oscillatory dynamics and long-range functional integration during cognitive control. The employed multimodal imaging approach combines magnetoencephalography (MEG) and structural magnetic resonance imaging (MRI) to provide insight into the neural basis of decision making with high temporal precision and at the level of an interactive system.

Flexible behavior makes it possible to adapt to changing contextual demands and to switch strategically between different tasks and requirements in agreement with one's intents and goals. The capacity to suppress automatic responses in favor of goal-relevant but non-habitual actions is an essential aspect of cognitive control. Extensive evidence suggests that it is subserved by a predominantly frontal cortical network, with the anterior cingulate cortex (ACC) as a central node in this interactive network[1-4]. While the abundant anatomical connectivity between the ACC and lateral frontal cortices is well-described[5,6], the functional characteristics of communication between these regions during cognitive control, response selection and execution, are poorly understood.

The highly influential conflict monitoring theory[7,8] proposes that cognitive control arises from a dynamic interaction between the medial and lateral prefrontal cortices. This account purports that the ACC monitors conflict between competing representations and engages the lateral prefrontal cortex (latPFC) to implement response control and optimize performance. However, this account is primarily based on the functional MRI (fMRI) studies using the blood oxygenation level dependent (BOLD) signal. The fMRI-BOLD signal is an excellent spatial mapping tool, but its temporal resolution is limited because it reflects regional hemodynamic changes mediated by neurovascular coupling. As a result, the BOLD signal changes unfold on a much slower time scale (in seconds) than the underlying neural events (in milliseconds)[9]. Moreover, the BOLD signal is sensitive to alcohol's vasoactive effects[10] and may not accurately represent the magnitude of neural changes, which makes it less suitable for studies of acute alcohol intoxication. Therefore, the presumed interplay between the medial and lateral prefrontal cortices and its sensitivity to alcohol intoxication need to be examined by methods

that record neural events in a temporally precise manner. MEG has an excellent temporal resolution since it directly reflects postsynaptic currents. The anatomically-constrained MEG (aMEG) methodology employed here is a multimodal approach that combines distributed source modeling of the MEG signal with structural MRI. It allows for the estimation of *where* the conflict- and beverage-related brain oscillatory changes are occurring and to understand the temporal sequence *("when")* of the involved neural components.

Decision making relies on the interactions of distributed brain regions that are dynamically engaged to deal with increased demands on cognitive control. One way to estimate event-related changes in long-range synchrony between two cortical regions is to calculate their phase coupling as an index of their co-oscillations[11,12]. The present study applied a phase-locking analysis to test the basic tenet of the conflict monitoring theory by examining the co-oscillatory interactions between the ACC and latPFC. Neural oscillations in theta range (4 - 7 Hz) are associated with cognitive control and have been proposed as a fundamental mechanism supporting the long-range synchronization needed for top-down cognitive processing[13-16]. They are generated in prefrontal areas as a function of task difficulty and are significantly attenuated by acute alcohol intoxication[17-20].

Long-term excessive alcohol intake is associated with a range of cognitive deficits with prefrontal circuitry being especially affected[21,22]. Acute alcohol intoxication is detrimental to cognitive control under conditions of increased difficulty, ambiguity, or those that induce response incompatibility[17,23,24]. By affecting decision making, alcohol may interfere with goal-directed behavior, may result in poor self-control and increased drinking, and may also contribute to traffic- or work-related hazards[25-27]. The present study uses an aMEG approach to measure the oscillatory activity in theta band and synchrony between the principal executive areas with excellent temporal resolution. The effects of alcohol on theta activity and co-oscillations between the ACC and the latPFC are examined as a function of conflict elicited by the Stroop interference task. We hypothesize that increased cognitive demands are associated with greater functional synchrony and that alcohol-induced dysregulation of synchronous activity of the medial and lateral prefrontal cortices underlies impairments in cognitive control.

PROTOCOL:

This experimental protocol has been approved by the Human Subjects Protection Committee at the University of California, San Diego.

1. Human Subjects

1.1. Recruit healthy right-handed adult volunteers, obtain their consent, and screen them on the inclusion/exclusion criteria.

NOTE: In this study, twenty young, healthy individuals (mean ± standard deviation [SD] age = 25.3 ± 4.4 years) including 8 women were recruited who drink in moderation, who have never been in treatment or arrested for drug or alcohol related offenses, who report no alcoholism-

related symptoms on the Short Michigan Alcoholism Screening Test[28], who do not smoke nor use illegal substances, who do not have a history of neuropsychiatric disorders or any current health problems, and who are medication free and have no internal ferromagnetic objects or implants.

2. Experimental Design

2.1. Scan each participant four times, including three MEG sessions (a no-beverage introductory session and two experimental beverage sessions in which alcohol and placebo are administered in a counterbalanced manner), and one structural MRI scan.

NOTE: In this within-subject design, participants serve as their own controls by participating in both alcohol and placebo sessions. This design reduces error variance and increases statistical power by minimizing influence of individual variability in brain anatomy, activity patterns, and alcohol metabolism.

3. Collecting MEG Scans

3.1. Perform familiarization session.

3.1.1. During the initial introductory session, administer questionnaires to obtain more information about the participants' medical history, their drinking patterns and severity of alcoholism-related symptoms[28,29], family history of alcoholism[30], and personality traits including impulsivity[31,32].

3.1.2. Carry out an initial recording in the MEG scanner following the protocol described below in steps 3.2, 3.3, and 3.5. Do not provide any beverage. Explain the task and run the practice version allowing participants to get familiarized with it beforehand.

NOTE: The acclimation to the experimental situation serves the purpose of minimizing potential effects of situation-induced arousal[33], thereby equating subsequent alcohol and placebo sessions on that dimension.

3.2. Perform the alcohol/placebo experimental sessions.

NOTE: Follow the same experimental procedures during both alcohol and placebo sessions with the exception of the administered beverage. Counterbalance beverage order by administering alcohol beverage first to one half of participants and placebo to the other half in a random order.

3.2.1. Upon their arrival to the MEG lab, run a brief test scan by putting the participant in the scanner and checking the channels for possible magnetization. Measure their weight. Screen them with an electronic breathalyzer. Query them about compliance with the requirements to abstain from alcohol for 48 h and from food for 3 h prior to the experiment.

3.2.2. Collect urine samples for a multi-drug test panel from all participants and exclude those who test positive for any drug. In addition, check female participants for pregnancy with a urine test and exclude those who test positive or if they suspect that they might be pregnant.

3.2.3. Assess dynamic changes in the subjective effects of alcohol by asking participants to rate their momentary feelings and states on a standardized scale[34] prior to drinking and on two additional occasions during the experiment - on the ascending limb (~15 min after consuming beverage) and descending limb of the breath alcohol concentration curve (BrAC), after the MEG recording.

3.2.4. Administer a practice run of the Stroop task on a laptop with stimulus presentation software to ensure that the participants understand the task before recording.

NOTE: This version of the Stroop task combines reading and color naming (**Figure 1**). The congruent condition consists of color words (*i.e.*, red, green, blue, yellow) that are printed in the matching font color (*i.e.*, the word "green" is printed in green). In the incongruous condition, color words are printed in color that does not match their meaning (*i.e.*, the word "green" is printed in yellow). Ask the participants to press one of four buttons corresponding to the font color whenever a word is written in color, or, when a word is written in gray, to press a button corresponding to the meaning of the word[18,23].

3.3. Prepare the magnetoencephalography/electroencephalographic (MEG/EEG) recording.

NOTE: Details of MEG data acquisition have been described in previous publications[35-37].

3.3.1. Position the EEG cap or individual EEG electrodes on the head of the participant and check that all impedances are below 5 kΩ.

3.3.2. Attach the head position indicator (HPI) coils on either side of the forehead and behind each ear.

NOTE: This step is specific to Neuromag systems.

3.3.3. Digitize positions of the fiducial points including the nasion and two preauricular points, positions of HPI coils, EEG electrodes, and obtain a large number of additional points (~200) delineating the head shape. Use this information for the co-registration with anatomical MRI images (**Figure 2**).

3.4. Administer beverage.

3.4.1. Prepare alcohol beverage by mixing premium quality vodka with chilled orange juice (25% v/v), based on each participant's gender and weight (0.60 g/kg alcohol for men, 0.55 g/kg alcohol for women), targeting a BrAC of 0.06%[38]. Serve the same volume of orange juice in

glasses with rims swabbed with vodka as a placebo beverage. Ask the participant to consume the beverage in approximately 10 min.

3.4.2. Check the participants' BrAC with the breathalyzer starting at ~15 min after drinking and then every 5 min until they enter the recording chamber. Since electronic devices cannot be used in the shielded room, use a saliva alcohol test, which consists of a cotton swab that is saturated in saliva and is inserted into a receptacle that provides a readout.

3.5. Acquire MEG/EEG data.

3.5.1. Position the participant comfortably in the scanner. Since the prefrontal activity is of particular interest, ensure that the participant is positioned so that his/her head is touching the top of the helmet and is aligned along the front.

NOTE: Head position can affect activity estimates in significant ways because the magnetic field gradients decrease with the cube of the distance between the sensors and the brain sources[39].

3.5.2. Connect HPI coils and all of the electrodes to their respective inputs on the scanner. Position response pads so that the buttons can be pressed comfortably. Ascertain that the font is clearly legible on the projection screen in front of the participant.

3.5.3. Back in the console room, check that the intercom is functioning properly. Remind the participant to minimize blinking and to avoid movements including head motion caused by talking. Instruct the participant to reply to questions by pressing response buttons instead.

3.5.4. Check that all response and stimulus triggers are recorded correctly. Examine all channels for artifacts and measure the head position in the scanner.

3.5.5. Start data acquisition and begin the task. Give breaks every ~2.5 min to rest the eyes. Save the data upon task completion and escort the participant out of the recording chamber.

3.5.6. When the participant has exited the scanner, acquire approximately two minutes of data from the empty room as a measure of instrumental noise.

3.5.7. Ask the participant to rate perceived task difficulty, content of the imbibed beverage, how intoxicated they felt, as well as their momentary moods and feelings[34].

4. Image Acquisition and Cortical Reconstruction of Structural MRI

4.1. Obtain a high-resolution anatomical MRI scan for each participant, and reconstruct each participant's cortical surface with FreeSurfer software[40-42].

4.2. Use the inner skull surface derived from the segmented structural MRI images to generate a boundary element model of the volume conductor, which is used to provide a model for the forward solution that is consistent with each individual's brain anatomy[43,44].

5. MEG Data Analysis

NOTE: Analyze the data with the anatomically-constrained MEG approach which uses each participant's reconstructed cortical surface to constrain source estimates to the cortical ribbon[40,45,46]. The analysis stream relies on custom functions with dependencies on publicly available packages including FieldTrip[47], EEGLab[48], and MNE[49].

5.1. During data preprocessing, use a permissive band-pass filter (*e.g.*, 0.1 - 100 Hz) and epoch data into segments that include padding intervals on each end (*e.g.*, -600 to 1100 ms for an interval of interest that spans -300 to 800 ms after stimulus onset).

5.2. Remove noisy and flat channels, as well as trials containing artifacts by visual inspection and using threshold-based rejection. Use independent component analysis[48] to remove eyeblink and heartbeat artifacts. Eliminate trials with incorrect responses.

5.3. Apply Morlet wavelets (**Figure 3**)[47] to calculate complex power spectrum for each trial in 1 Hz increments for theta frequency band (4 - 7 Hz). Remove any additional artifacts. Compute the noise covariance from empty room data.

5.4. Co-register the MEG data with MRI images using the three-dimensional (3D) head digitization information (**Figure 2**).

5.4.1. Open the MRIlab module.

5.4.2. Select **File| Open| Select subject's structural MRI**.

5.4.3. Select **File| Import| Isotrak data| select raw data.fif file| Make Points**.

5.4.4. Select **Windows| Landmarks| Adjust fiducial landmarks** until co-registration of MEG data and MRI are acceptable.

5.4.5. Select **File| Save**.

5.5. Calculate noise-sensitivity normalized estimates of theta source power and phase with a spectral dynamic statistical mapping approach[18,50]. Express event-related theta source power as percent signal change relative to baseline.

5.6. Create group averages of event-related theta source power by morphing each participant's estimates onto an average cortical representation[51].

5.7. Visualize the source estimates on an inflated average surface to enhance visibility of sulcal estimates (**Figure 4**).

5.7.1. Open the MNE software.

5.7.2. Select **File| Load Surface| Load inflated group-average FreeSurfer cortical surface**.

5.7.3. Select **File| Manage overlays| Load stc| Load group-averaged data| Select loaded file from available overlays**.

5.7.4. Select overlay type as **Other**.

5.7.5. Adjust **Color Scale thresholding| Show**.

5.7.6. View **brain movies** and examine spatio-temporal stages of processing by identifying areas and time windows characterized by highest activation.

5.8. Create unbiased regions of interest (ROIs) based on overall group-averaged estimates to incorporate cortical locations with most notable source power. Calculate time courses for each subject, condition, and ROI (**Figure 5**).

5.9. Submit the obtained theta source power estimates to the statistical analysis.

5.9.1. Extract time windows of interest from each ROI time course and perform analysis of variance (ANOVA) with beverage (alcohol, placebo) and trial type (congruent, incongruous) as within subject factors. Use a nonparametric cluster-based permutation test[52] to examine beverage and condition comparisons of event-related theta power as well as phase-locking value (PLV).

5.10. Estimate task-related changes in the long-range synchronization between the main activation foci in the ACC and the latPFC by computing the PLV[12]. Express PLV as percent change relative to baseline.

NOTE: The PLV is an indicator of consistency of the phase angle between the two ROIs across trials as it measures the extent to which they co-oscillate at a particular frequency and in real time (**Movie 1**).

5.11. Calculate correlations between ROI MEG activity estimates, indices of behavioral performance, and questionnaire scores to inform interpretation of the observed results.

REPRESENTATIVE RESULTS:

Behavioral results indicate that the Stroop task successfully manipulated response interference because the accuracy was the lowest and the response times the longest on incongruous trials (**Figure 6**). Alcohol intoxication lowered accuracy but did not affect reaction times[18].

The spatio-temporal sequence of activity in theta frequency band revealed with the aMEG approach is overall in agreement with generally accepted models of cognitive functions in this type of task. As illustrated in the brain movies (**Movie 2**), the visual cortex is activated at around 100 ms after stimulus onset, followed by a posterior-to-anterior activation pattern that engages primarily frontal cortices during cognitive integration stages after ~300 ms. The ACC is particularly sensitive to incongruous, high-conflict trials, indicating its engagement during conflict monitoring. The ACC is the principal generator of theta oscillations during tasks probing cognitive control but the latPFC is also active during the integration stage at around 350-600 ms. Activation of the motor cortex is visible after ~600 ms during the response preparation stage (**Movie 2B**). Event-related theta power is greatest on incongruous (INC) trials, which is consistent with its sensitivity to conflict demands (**Figure 5**), especially in the prefrontal cortex[13,17,19,20]. Theta power is decreased by acute alcohol intoxication overall. However, when compared to congruous (CONG) trials, alcohol decreases theta power on incongruous (high conflict) trials selectively in the ACC and latPFC[18].

The present study extends the results from Kovacevic *et al.*[18] by focusing on dynamic interactions between these areas during the processing of Stroop interference in light of a prevailing account of the cognitive control network[7,8]. To better understand the timing, degree, and nature of the interactions between these two principally engaged cortical areas, the PLV was calculated for each beverage and task condition, and for each participant. As shown in a group average in **Figure 7**, co-oscillations between the ACC and latPFC vary across time with an overall early increase in co-oscillations during a stimulus processing stage. Under placebo, this is followed by a sustained increase after ~400 ms on incongruous trials during the integration and response preparation stage. Thus, synchronized co-oscillations between the medial and lateral prefrontal cortices are observed only on the more difficult, incongruous trials evoking response conflict $F(1,19) = 5.5$, $p < 0.05$. This evidence supports the proposal that the ACC and the latPFC functionally interact in real time to subserve cognitive control. In contrast, acute alcohol intoxication significantly dysregulates the co-oscillations, yielding a Condition x Beverage interaction, $F(1,19) = 5.1$, $p < 0.05$, in which incongruous trials specifically were affected by alcohol $F(1,19) = 8.8$, $p < 0.01$ (**Figure 7**). This may underlie alcohol-induced impairments of inhibitory control and indicates the vulnerability of top-down regulative functions of the prefrontal cortex to acute intoxication.

FIGURE AND TABLE LEGENDS:

Figure 1: Stroop task combines color naming and reading. Trial examples for each of the three conditions along with the correct response color are presented. In the congruent condition (CONG), font color is consistent with the word meaning, while incongruous trials (INC) elicit response conflict due to interference from word meaning. Participants are instructed to press a button corresponding to the font color when words are written in color (CONG, INC) and to respond to the word meaning (Read) when they are written in gray. Trials are presented for 300 ms and then replaced by a fixation screen for 1700 ms. Trial types are presented in a

randomized order. In this particular version, the CONG and INC conditions were equiprobable and were presented on 16.7% trials each out of 576 trials total.

Figure 2: Co-registration of MEG and MRI. Digitized points across the head collected during the MEG recording are used for co-registration with anatomical MRI images.

Figure 3: Morlet wavelet. Morlet wavelets are used to calculate complex power spectrum for each trial in 1 Hz frequency increments for the theta band frequency (4 - 7 Hz).

Figure 4: Cortical reconstruction and inflation. Individual cortical surfaces are reconstructed and are used to constrain estimated source power. Here shown is an average cortical surface which is inflated to enhance visibility of the sources estimated to cortical sulci.

Figure 5: Group-average time courses of event-related theta source power estimates in selected regions of interest. Incongruous stimuli (INC) elicited increased event-related theta power compared to congruent stimuli (CONG) in the anterior cingulate cortex (ACC; $F(1,19) = 34.1$, $p < 0.0001$) as well as the lateral prefrontal cortex (latPFC; $F(1,19) = 11.0$, $p < 0.01$), during 480 - 670 ms. Conflict processing is particularly sensitive to alcohol intoxication as theta power to INC was attenuated by alcohol intoxication ($F(1,19) = 9.9$, $p < 0.01$). The y-axis depicts baseline-corrected noise-normalized event-related theta source power. This figure has been modified from Kovacevic *et al.*[18].

Figure 6: Behavioral results on the Stroop task. Stroop interference was reflected in decreased accuracy and longer response times to incongruous (INC) trials. Alcohol intoxication (Alc) impaired accuracy compared to placebo (Plac) but did not affect reaction times. Error bars signify standard error of the mean. This figure has been modified from Kovacevic *et al.*[18].

Figure 7: Group-average time courses of phase-locking values (PLVs) in the theta band. Co-oscillatory synchrony between the anterior cingulate cortex (ACC) and lateral prefrontal cortex (latPFC) in theta band expressed as percent change from baseline for placebo (left) and alcohol (right) conditions. Following an early increase in PLVs during a stimulus processing stage (400 - 600 ms), a sustained increase in co-oscillations is observed on incongruous trials (INC) in response to increased cognitive control compared to congruent trials (CONG) under placebo, $F(1,19) = 5.5$, $p < 0.05$. Acute alcohol intoxication selectively dysregulated the co-oscillations on INC trials, $F(1,19) = 8.8$, $p < 0.01$. Activation maps (inset) show the incongruity effect (INC-CONG), which is prominent in the ACC and latPFC. The color scale denotes baseline-corrected source power estimates at 480 ms after stimulus onset, with red (activity > 0.2) to yellow (activity > 0.3) indicating stronger theta power to INC trials compared to CONG trials.

Movie 1: Co-oscillations. Phase-locking values were calculated in the theta frequency range (4 - 7 Hz) between the anterior cingulate cortex (ACC) and lateral prefrontal cortex (latPFC) as a measure of synchronization that is sensitive to the consistency of the phase difference between these two ROIs regardless of their theta power amplitude.

Movie 2: Brain movies. Distributed source modeling of the MEG signal combined with structural MRI allows for the estimation of principal cortical areas generating theta power and the temporal sequence of their activation in response to the Stroop interference. (**A**) Following early sensory processing, the anterior cingulate cortex (ACC) is selectively activated by incongruous, high-conflict trials after ~350 ms. (**B**) While the ACC is the principal generator of theta oscillations during tasks probing cognitive control, the lateral prefrontal cortex (latPFC) is also engaged during the integration stage around 350 - 600 ms. Activation of the motor cortex is observed after ~600 ms during response preparation. The color scale denotes differential baseline-corrected source power estimates, with red color indicating activation greater than 0.79 medially (0.57 laterally) and yellow indicates activation greater than 0.9 medially (0.8 laterally). Please note that these two movies should be shown together with unfolding time courses pertaining to the ACC and latPFC, respectively.

DISCUSSION:

The multimodal imaging method used in this study comprises distributed source modeling of the temporally precise MEG signal along with spatial constraints of inverse estimates derived from each participant's structural MRI. The aMEG approach combines the strengths of these techniques to provide insight into the spatio-temporal stages of oscillatory dynamics and the long-range integration subserving cognitive control. This method provides greater temporal precision than other neuroimaging techniques such as fMRI-BOLD whose temporal resolution is on the magnitude of seconds due to its indirect sensitivity to neural changes via neurovascular coupling[9]. In comparison, the millisecond precision of MEG signal allows for the investigation of neural processing stages, as demonstrated by the present study. The aMEG model assumes distributed sources of the MEG signal along the cortical surface which, when reconstructed from structural MRI images, provides spatial constraints for activity estimates[45,53]. These spatial estimates can be used to investigate not only local activation but long-range communication at an interactive network level in the form of phase-locking[16,20]. Moreover, the aMEG approach is well suited for investigating the effects of pharmacological manipulation on neural functions, given that the fMRI-BOLD signal is confounded by the vasoactive effects of pharmacological manipulations such as alcohol and may not accurately reflect the magnitude of neural changes[10].

The high sensitivity of this method to minute neural changes means that it is also sensitive to non-neural noise including muscle movements or eye blinks, so the various artifacts need to be detected and carefully removed from the raw signal. Moreover, head position can have significant effects on activity estimates due to sensor sensitivity to magnetic field gradients[39]. Given the assumptions of the aMEG model, source estimates are constrained to the cortical surface[45,46], so the activity elicited from subcortical structures cannot be estimated.

Based on previously published results[18], the present study has illustrated changes in event-related theta (4 - 7 Hz) power during Stroop-induced conflict as a function of acute alcohol intoxication in healthy social drinkers. As shown in **Figure 5**, theta power is differentially sensitive to cognitive demands imposed by the Stroop task conditions. Incongruity is especially effective in engaging cognitive control as reflected in greater theta power in the prefrontal

cortex compared to prestimulus baseline. The principal estimated generator of theta oscillations is the ACC that is sensitive to response conflict during both early and late processing stages[18]. These findings support the role of the ACC in monitoring for conflict in concordance with prominent accounts[7,8]. Thus, the aMEG method has provided a temporally-sensitive insight into the sustained engagement of the ACC during trials imposing higher load on cognitive control. Together with extensive anatomical connections between the ACC and distributed brain regions[5,6], this evidence corroborates its multifaceted role in self-regulation. On that view, the ACC is a key hub in the neurofunctional system that subserves cognitive control by aligning goals and intentions with contextual and motivational constraints[54,55]. Inferolateral prefrontal cortex, especially on the right, is another important area within that system which has been associated with inhibition of prepotent responses, attentional control, and working memory in the service of updating task representations[56-58].

It has been established that theta oscillations mediate neural integration necessary for cognitive and affective processing[13,16,59,60]. Neural communication may thus rely on synchronized excitability of distant neuronal ensembles in theta band with nested fast rhythms mediating local processing[61,62]. PLVs reflect phase consistency between cortical areas and are commonly used to estimate their oscillatory synchrony as it is assumed that two areas interact when they co-oscillate[63]. Indeed, transient increases in PLV are observed in those intervals of neural activity that would be expected to necessitate synchronous interactions[12,20]. The present study confirms previous evidence and adds spatio-temporal refinement to the functional synchronization between the sources estimated to the ACC and the latPFC. Consistent with previous reports[64], the present results indicate that PLVs are increased and sustained on incongruous trials in the Stroop task. By quantifying phase synchronization between these two areas with high temporal precision, these findings extend the conflict monitoring account and indicate that their interaction is particularly prominent after ~350 ms on incongruous trials. During this cognitive integration stage, the medial and lateral prefrontal cortices are likely to interact to support behavioral performance during more difficult task conditions imposing demands on attention, response inhibition, and working memory. Extensive evidence from MRI-based functional connectivity studies indicates that these cortical areas form a dynamic, interactive cingulo-opercular network that supports top-down cognitive control[65-67]. More broadly, the brain optimizes responding to environmental demands in an adaptive and coherent manner *via* flexible and dynamic synchronization of distributed neurofunctional systems[68,69].

The anatomically-constrained MEG approach used in the present study relies on a combination of complementary imaging methods. It can characterize the spatio-temporal sequence of neural activity and can provide insight into the dynamics of long-range interactions important for integrating top-down influences during engagement of cognitive control. The MEG signal reflects synaptic currents directly, which allows for testing hypotheses about co-oscillatory interactions within and across neurofunctional systems with high temporal precision. Furthermore, this method is suitable for pharmacological manipulations because it is not susceptible to vasoactive confounds. Research from this lab and others indicates that prefrontally-mediated cognitive control functions are particularly vulnerable to alcohol

intoxication[17-20,23,24,70-74]. The present study shows that acute alcohol intoxication decreases activity in the prefrontal areas subserving response conflict. Furthermore, alcohol disrupts synchronized co-oscillations[20,75] that may underlie impaired or maladaptive response suppression. As a result, intoxicated individuals exhibit deficient self-control resulting in disinhibition which may contribute to compulsive drinking and the development of alcohol dependence[25,26,76]. In sum, estimates of synchronous co-oscillations can illuminate real-time interactions of the neural systems engaged by a particular cognitive demand and can inform a realistic brain-based model. They can characterize the selective sensitivity to alcohol challenge across networks and serve as biomarkers of individual vulnerability to pharmacological effects.

ACKNOWLEDGMENTS:

This work has been supported by the National Institutes of Health (R01-AA016624). We are grateful to Dr. Sanja Kovacevic for her important contributions.

DISCLOSURES:

The authors have nothing to disclose.

REFERENCES:

1 Ridderinkhof, K. R., van den Wildenberg, W. P., Segalowitz, S. J., Carter, C. S. Neurocognitive mechanisms of cognitive control: the role of prefrontal cortex in action selection, response inhibition, performance monitoring, and reward-based learning. *Brain and Cognition.* **56** (2), 129-140 (2004).

2 Shenhav, A., Cohen, J. D., Botvinick, M. M. Dorsal anterior cingulate cortex and the value of control. *Nature Neuroscience.* **19** (10), 1286-1291 (2016).

3 Walton, M. E., Croxson, P. L., Behrens, T. E., Kennerley, S. W., Rushworth, M. F. Adaptive decision making and value in the anterior cingulate cortex. *Neuroimage.* **36 Suppl 2**, T142-154 (2007).

4 Heilbronner, S. R., Hayden, B. Y. Dorsal Anterior Cingulate Cortex: A Bottom-Up View. *Annual Review of Neuroscience.* **39** 149-170 (2016).

5 Barbas, H. Connections underlying the synthesis of cognition, memory, and emotion in primate prefrontal cortices. *Brain Research Bulletin.* **52** (5), 319-330 (2000).

6 Morecraft, R. J., Tanji, J. in *Cingulate neurobiology and disease* (ed B. A. Vogt) 114-144 (Oxford University Press, 2009).

7 Botvinick, M. M. Conflict monitoring and decision making: reconciling two perspectives on anterior cingulate function. *Cognitive, Affective, & Behavioral Neuroscience.* **7** (4), 356-366 (2007).

8 Carter, C. S., van Veen, V. Anterior cingulate cortex and conflict detection: an update of theory and data. *Cognitive, Affective, & Behavioral Neuroscience.* **7** (4), 367-379 (2007).

9 Buxton, R. B. *Introduction to Functional Magnetic Resonance Imaging*. (Cambridge University Press, New York, NY, 2002).

10 Rickenbacher, E., Greve, D. N., Azma, S., Pfeuffer, J., Marinkovic, K. Effects of alcohol intoxication and gender on cerebral perfusion: an arterial spin labeling study. *Alcohol.* **45** (8), 725-737 (2011).

11 Fell, J., Axmacher, N. The role of phase synchronization in memory processes. *Nature Reviews Neuroscience* **12** (2), 105-118 (2011).

12 Lachaux, J. P., Rodriguez, E., Martinerie, J., Varela, F. J. Measuring phase synchrony in brain signals. *Human Brain Mapping.* **8** (4), 194-208 (1999).

13 Cavanagh, J. F., Frank, M. J. Frontal theta as a mechanism for cognitive control. *Trends in Cognitive Sciences.* **18** (8), 414-421 (2014).

14 Sauseng, P., Griesmayr, B., Freunberger, R., Klimesch, W. Control mechanisms in working memory: a possible function of EEG theta oscillations. *Neuroscience & Biobehavioral Reviews* **34** (7), 1015-1022 (2010).

15 Wang, C., Ulbert, I., Schomer, D. L., Marinkovic, K., Halgren, E. Responses of human anterior cingulate cortex microdomains to error detection, conflict monitoring, stimulus-response mapping, familiarity, and orienting. *The Journal of Neuroscience.* **25** (3), 604-613 (2005).

16 Halgren, E. *et al.* Laminar profile of spontaneous and evoked theta: Rhythmic modulation of cortical processing during word integration. *Neuropsychologia.* **76** 108-124 (2015).

17 Rosen, B. Q., Padovan, N., Marinkovic, K. Alcohol hits you when it is hard: Intoxication, task difficulty, and theta brain oscillations. *Alcoholism: Clinical and Experimental Research.* **40** (4), 743-752 (2016).

18 Kovacevic, S. *et al.* Theta oscillations are sensitive to both early and late conflict processing stages: effects of alcohol intoxication. *PLoS One.* **7** (8), e43957 (2012).

19 Marinkovic, K., Rosen, B. Q., Cox, B., Kovacevic, S. Event-related theta power during lexical-semantic retrieval and decision conflict is modulated by alcohol intoxication: Anatomically-constrained MEG. *Frontiers in Psychology.* **3** (121) (2012).

20 Beaton, L. E., Azma, S., Marinkovic, K. When the brain changes its mind: Oscillatory dynamics of conflict processing and response switching in a flanker task during alcohol challenge. *PLoS One.* **13** (1), e0191200 (2018).

21 Oscar-Berman, M., Marinkovic, K. Alcohol: effects on neurobehavioral functions and the brain. *Neuropsychology Review.* **17** (3), 239-257 (2007).

22 Le Berre, A. P., Fama, R., Sullivan, E. V. Executive Functions, Memory, and Social Cognitive Deficits and Recovery in Chronic Alcoholism: A Critical Review to Inform Future Research. *Alcoholism: Clinical and Experimental Research.* **41** (8), 1432-1443 (2017).

23 Marinkovic, K., Rickenbacher, E., Azma, S., Artsy, E. Acute alcohol intoxication impairs top-down regulation of Stroop incongruity as revealed by blood oxygen level-dependent functional magnetic resonance imaging. *Human Brain Mapping.* **33** (2), 319-333 (2012).

24 Marinkovic, K., Rickenbacher, E., Azma, S., Artsy, E., Lee, A. K. Effects of acute alcohol intoxication on saccadic conflict and error processing. *Psychopharmacology (Berl).* **230** (3), 487-497 (2013).

25 Field, M., Wiers, R. W., Christiansen, P., Fillmore, M. T., Verster, J. C. Acute alcohol effects on inhibitory control and implicit cognition: implications for loss of control over drinking. *Alcoholism: Clinical and Experimental Research.* **34** (8), 1346-1352 (2010).

26 Fillmore, M. T. Drug abuse as a problem of impaired control: current approaches and findings. *Behavioral and Cognitive Neuroscience Reviews.* **2** (3), 179-197 (2003).

27 Hingson, R., Winter, M. Epidemiology and consequences of drinking and driving. *Alcohol Reseach & Health.* **27** (1), 63-78 (2003).

28 Selzer, M. L., Vinokur, A., Van Rooijen, L. A self-administered Short Michigan Alcoholism Screening Test (SMAST). *Journal of Studies on Alcohol.* **36** (1), 117-126 (1975).

29 Babor, T., Higgins-Biddle, J. S., Saunders, J. B., Monteiro, M. G. AUDIT: The Alcohol use disorders identification test: Guidelines for use in primary care. (WHO: World Health Organization, Geneva, Switzerland, 2001).

30 Rice, J. P. *et al.* Comparison of direct interview and family history diagnoses of alcohol dependence. *Alcoholism: Clinical and Experimental Research.* **19** (4), 1018-1023 (1995).

31 Eysenck, H. J., Eysenck, S. B. G. *Manual of the Eysenck Personality Questionnaire*. (Hodder & Staughton, 1975).

32 Eysenck, S. B., Eysenck, H. J. Impulsiveness and venturesomeness: their position in a dimensional system of personality description. *Psychological Reports.* **43** (3 Pt 2), 1247-1255 (1978).

33 Maltzman, I., Marinkovic, K. in *The Pharmacology of Alcohol and Alcohol Dependence* eds H. Begleiter & B. Kissin) 248-306 (Oxford University Press, 1996).

34 Martin, C. S., Earleywine, M., Musty, R. E., Perrine, M. W., Swift, R. M. Development and validation of the Biphasic Alcohol Effects Scale. *Alcoholism: Clinical and Experimental Research.* **17** (1), 140-146. (1993).

35 Liu, H., Tanaka, N., Stufflebeam, S., Ahlfors, S., Hamalainen, M. Functional Mapping with Simultaneous MEG and EEG. *Journal of Visualized Experiments.* 10.3791/1668 [pii] (40), (2010).

36 Lee, A. K., Larson, E., Maddox, R. K. Mapping cortical dynamics using simultaneous MEG/EEG and anatomically-constrained minimum-norm estimates: an auditory attention example. *Journal of Visualized Experiments.* 10.3791/4262 [pii] (68), e4262 (2012).

37 Balderston, N. L., Schultz, D. H., Baillet, S., Helmstetter, F. J. How to detect amygdala activity with magnetoencephalography using source imaging. *Journal of Visualized Experiments.* 10.3791/50212 (76), (2013).

38 Breslin, F. C., Kapur, B. M., Sobell, M. B., Cappell, H. Gender and alcohol dosing: a procedure for producing comparable breath alcohol curves for men and women. *Alcoholism: Clinical and Experimental Research.* **21** (5), 928-930 (1997).

39 Marinkovic, K., Cox, B., Reid, K., Halgren, E. Head position in the MEG helmet affects the sensitivity to anterior sources. *Neurology and Clinical Neurophysiology.* **2004**, 30 (2004).

40 Dale, A. M., Sereno, M. I. Improved localization of cortical activity by combining EEG and MEG with MRI cortical surface reconstruction: A linear approach. *Journal of Cognitive Neuroscience.* **5** 162-176 (1993).

41 Dale, A. M., Fischl, B., Sereno, M. I. Cortical surface-based analysis. I. Segmentation and surface reconstruction. *Neuroimage.* **9** (2), 179-194 (1999).

42 Fischl, B., Sereno, M. I., Dale, A. M. Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. *Neuroimage.* **9** (2), 195-207 (1999).

43 Gramfort, A., Papadopoulo, T., Olivi, E., Clerc, M. OpenMEEG: opensource software for quasistatic bioelectromagnetics. *Biomedical Engineering Online.* **9**, 45 (2010).

44 Kybic, J. *et al.* A common formalism for the integral formulations of the forward EEG problem. *IEEE Transactions on Medical Imaging.* **24** (1), 12-28 (2005).

45 Dale, A. M. *et al.* Dynamic statistical parametric mapping: combining fMRI and MEG for high-resolution imaging of cortical activity. *Neuron.* **26** (1), 55-67 (2000).

46 Marinkovic, K. Spatiotemporal dynamics of word processing in the human cortex. *The Neuroscientist.* **10** (2), 142-152 (2004).

47 Oostenveld, R., Fries, P., Maris, E., Schoffelen, J. M. FieldTrip: Open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. *Computational Intelligence and Neuroscience.* **2011**, 156869 (2011).

48 Delorme, A., Makeig, S. EEGLAB: An open source toolbox for analysis of single-trial EEG dynamics. *Journal of Neuroscience Methods.* **134**, 9-21 (2004).

49 Gramfort, A. *et al.* MNE software for processing MEG and EEG data. *Neuroimage.* **86**, 446-460 (2014).

50 Lin, F. H. *et al.* Spectral spatiotemporal imaging of cortical oscillations and interactions in the human brain. *Neuroimage.* **23** (2), 582-595 (2004).

51 Fischl, B., Sereno, M. I., Tootell, R. B., Dale, A. M. High-resolution intersubject averaging and a coordinate system for the cortical surface. *Human Brain Mapping.* **8** (4), 272-284 (1999).

52 Maris, E., Oostenveld, R. Nonparametric statistical testing of EEG- and MEG-data. *Journal of Neuroscience Methods.* **164** (1), 177-190 (2007).

53 Marinkovic, K. *et al.* Spatiotemporal dynamics of modality-specific and supramodal word processing. *Neuron.* **38** (3), 487-497 (2003).

54 Nachev, P. Cognition and medial frontal cortex in health and disease. *Current Opinion in Neurology.* **19** (6), 586-592 (2006).

55 Kennerley, S. W., Walton, M. E., Behrens, T. E., Buckley, M. J., Rushworth, M. F. Optimal decision making and the anterior cingulate cortex. *Nature Neuroscience* **9** (7), 940-947 (2006).

56 Aron, A. R., Robbins, T. W., Poldrack, R. A. Inhibition and the right inferior frontal cortex: one decade on. *Trends in Cognitive Sciences.* **18** (4), 177-185 (2014).

57 Erika-Florence, M., Leech, R., Hampshire, A. A functional network perspective on response inhibition and attentional control. *Nature Communications.* **5**, 4073 (2014).

58 D'Esposito, M., Postle, B. R. The cognitive neuroscience of working memory. *Annual Review of Psychology.* **66** 115-142 (2015).

59 Hasselmo, M. E., Stern, C. E. Theta rhythm and the encoding and retrieval of space and time. *Neuroimage.* **85 Pt 2**, 656-666 (2014).

60 Womelsdorf, T., Johnston, K., Vinck, M., Everling, S. Theta-activity in anterior cingulate cortex predicts task rules and their adjustments following errors. *Proceedings of the National Academy of Sciences of the United States of America*. **107** (11), 5248-5253 (2010).

61 Fries, P. A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. *Trends in Cognitive Sciences.* **9** (10), 474-480 (2005).

62 Canolty, R. T. *et al.* High gamma power is phase-locked to theta oscillations in human neocortex. *Science.* **313** (5793), 1626-1628 (2006).

63 Varela, F., Lachaux, J. P., Rodriguez, E., Martinerie, J. The brainweb: phase synchronization and large-scale integration. *Nature Reviews Neuroscience* **2** (4), 229-239 (2001).
64 Hanslmayr, S. *et al.* The electrophysiological dynamics of interference during the Stroop task. *Journal of Cognitive Neuroscience.* **20** (2), 215-225 (2008).
65 Niendam, T. A. *et al.* Meta-analytic evidence for a superordinate cognitive control network subserving diverse executive functions. *Cognitive, Affective, & Behavioral Neuroscience.* **12** (2), 241-268 (2012).
66 Sadaghiani, S., D'Esposito, M. Functional Characterization of the Cingulo-Opercular Network in the Maintenance of Tonic Alertness. *Cerebral Cortex.* **25** (9), 2763-2773 (2015).
67 Dosenbach, N. U., Fair, D. A., Cohen, A. L., Schlaggar, B. L., Petersen, S. E. A dual-networks architecture of top-down control. *Trends in Cognitive Sciences.* **12** (3), 99-105 (2008).
68 Bullmore, E., Sporns, O. The economy of brain network organization. *Nature Reviews Neuroscience.* **13** (5), 336-349 (2012).
69 Fornito, A., Zalesky, A., Breakspear, M. The connectomics of brain disorders. *Nature Reviews Neuroscience.* **16** (3), 159-172 (2015).
70 Anderson, B. M. *et al.* Functional imaging of cognitive control during acute alcohol intoxication. *Alcoholism: Clinical and Experimental Research.* **35** (1), 156-165 (2011).
71 Kareken, D. A. *et al.* Family history of alcoholism interacts with alcohol to affect brain regions involved in behavioral inhibition. *Psychopharmacology (Berl).* **228** (2), 335-345 (2013).
72 Schuckit, M. A. *et al.* fMRI differences between subjects with low and high responses to alcohol during a stop signal task. *Alcoholism: Clinical and Experimental Research.* **36** (1), 130-140 (2012).
73 Nikolaou, K., Critchley, H., Duka, T. Alcohol affects neuronal substrates of response inhibition but not of perceptual processing of stimuli signalling a stop response. *PLoS One.* **8** (9), e76649 (2013).
74 Gan, G. *et al.* Alcohol-induced impairment of inhibitory control is linked to attenuated brain responses in right fronto-temporal cortex. *Biology Psychiatry.* **76** (9), 698-707 (2014).
75 Ehlers, C. L., Wills, D. N., Havstad, J. Ethanol reduces the phase locking of neural activity in human and rodent brain. *Brain Research.* **1450**, 67-79 (2012).
76 Goldstein, R. Z., Volkow, N. D. Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. *Nature Reviews Neuroscience* **12** (11), 652-669 (2011).

Figure 1

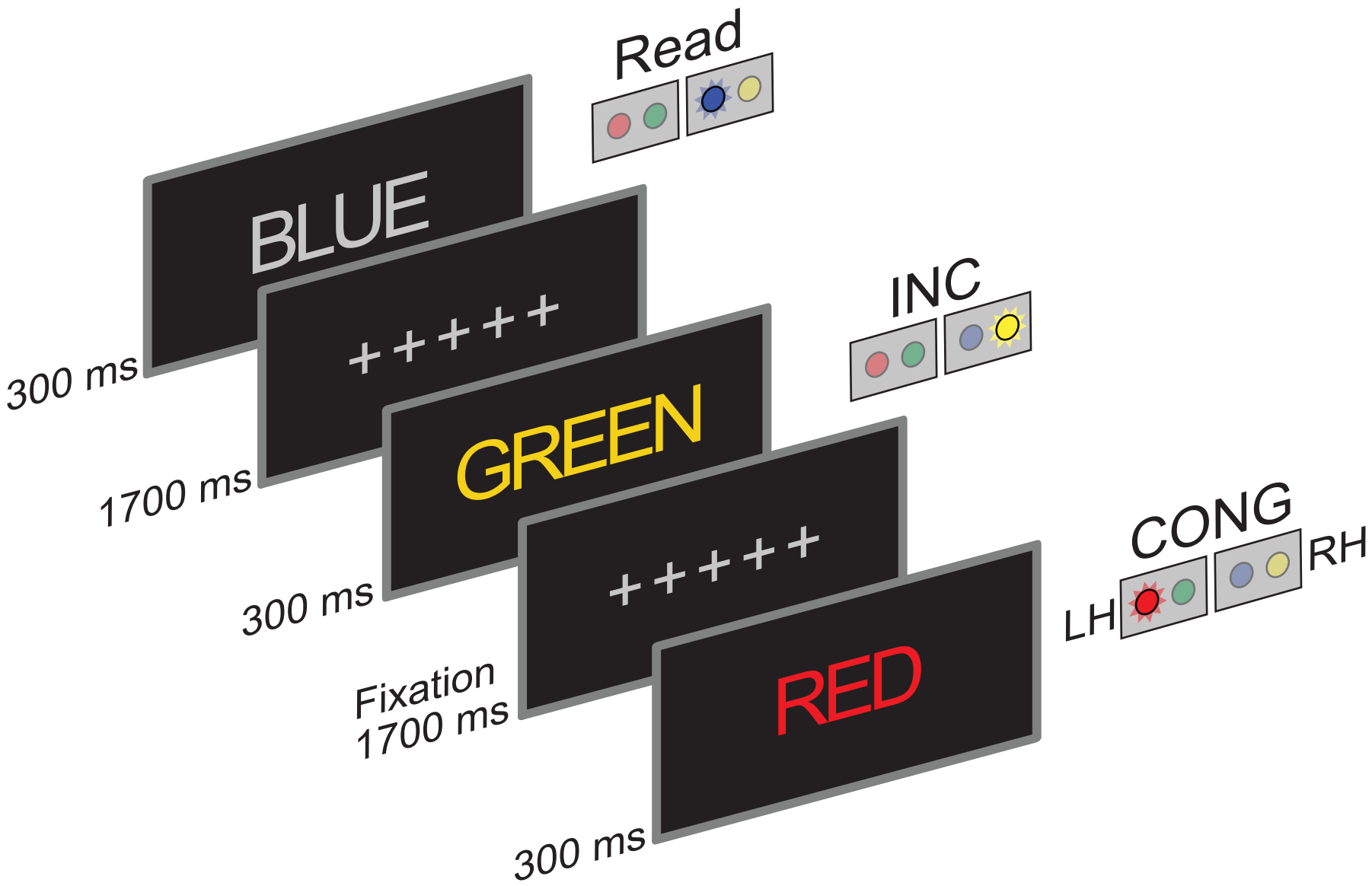


Figure 2

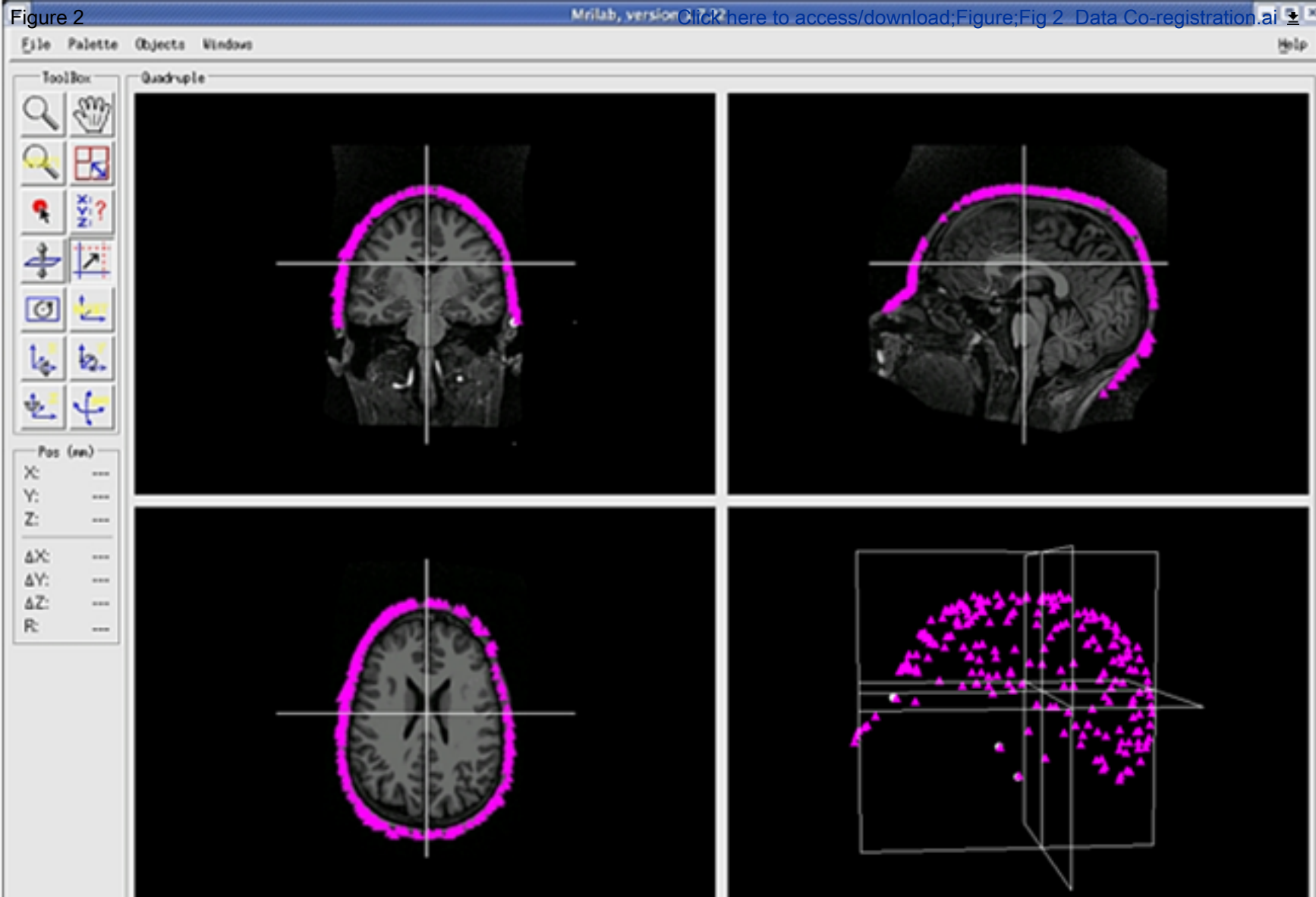


Figure 3

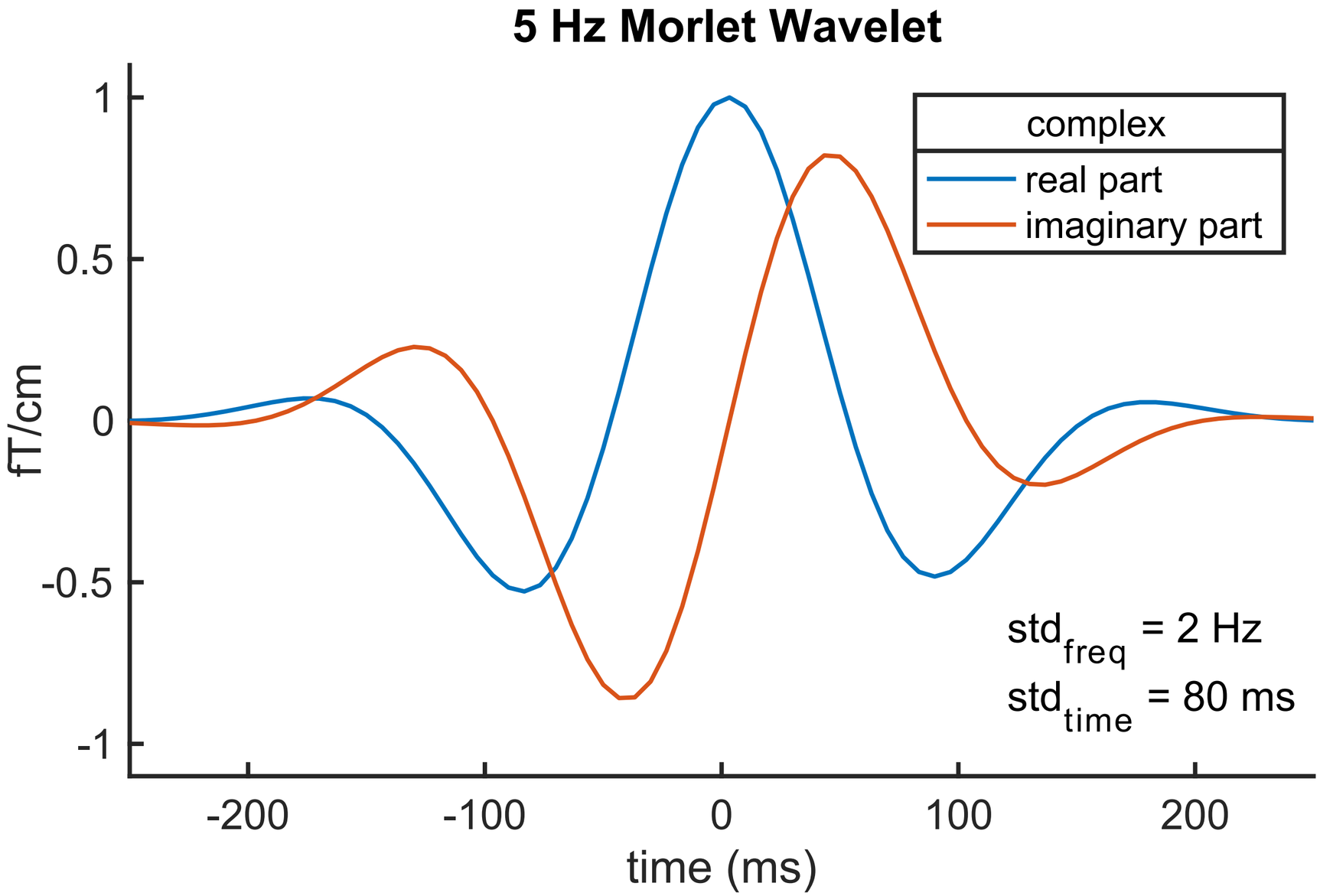


Figure 4

Click here to access/download;Figure;Fig 4 Cortical Surface Inflation.ai

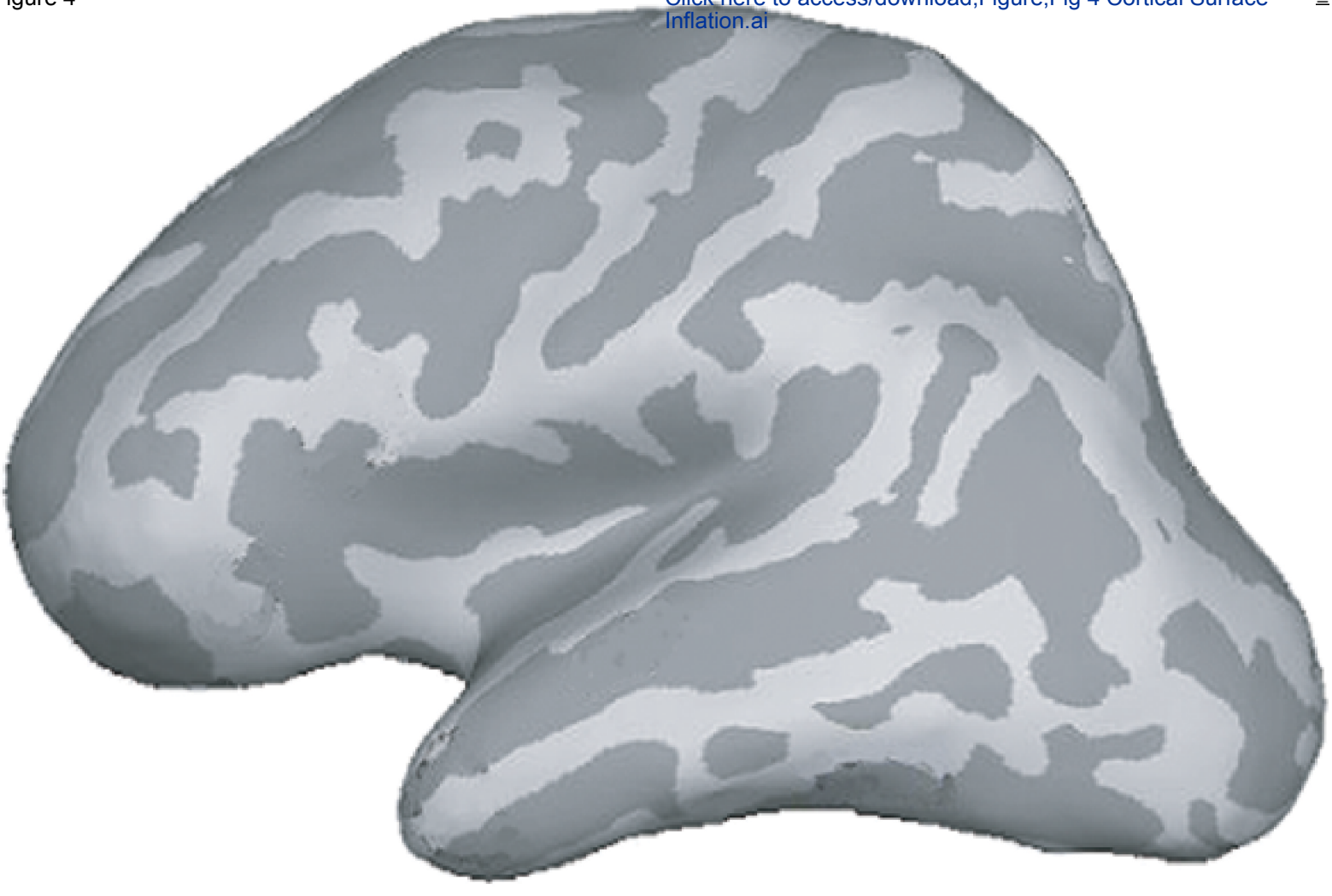


Figure 5

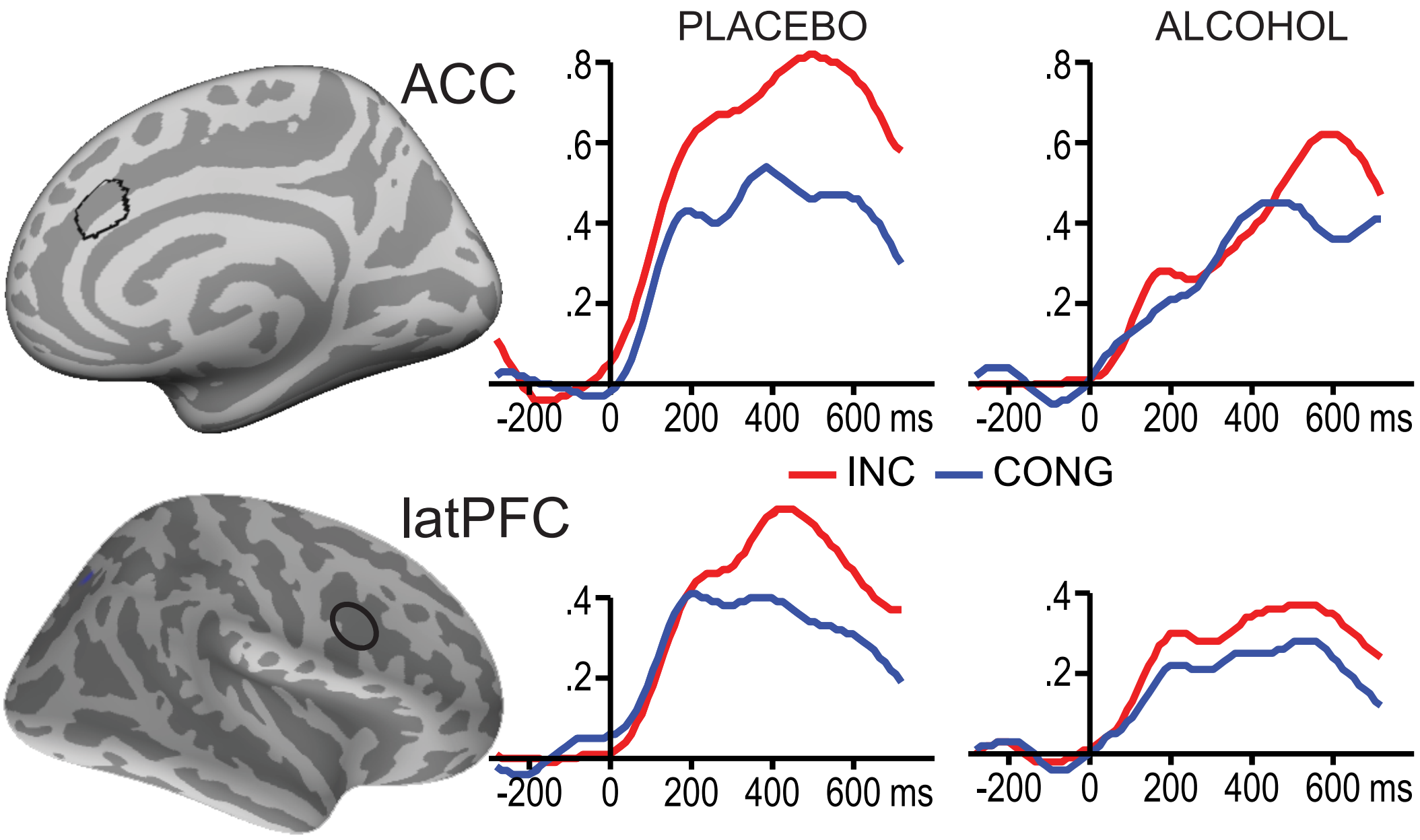


Figure 6

Click here to access/download;Figure;Fig 6 Behavioral Results.ai

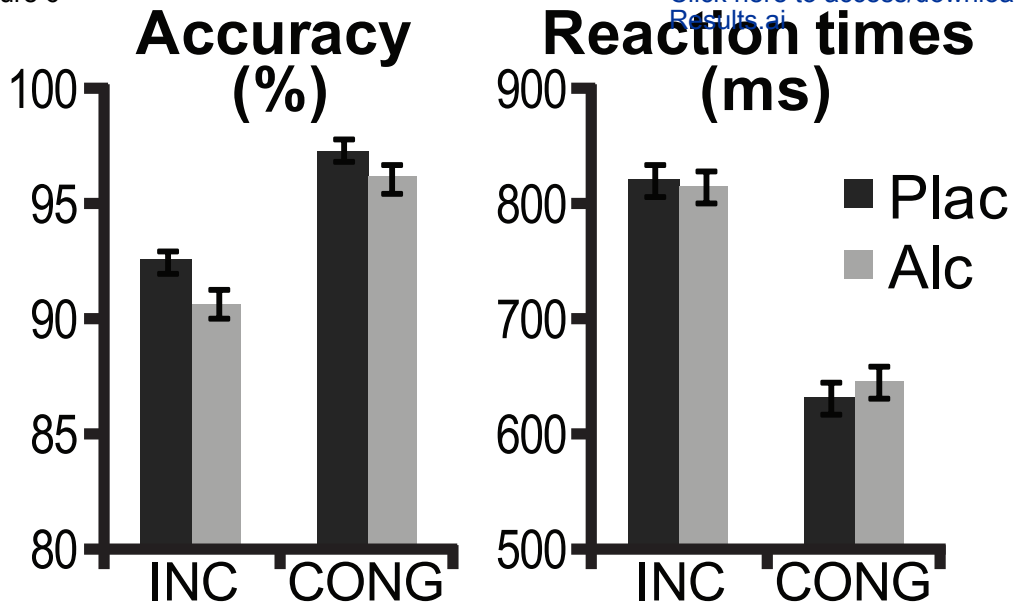
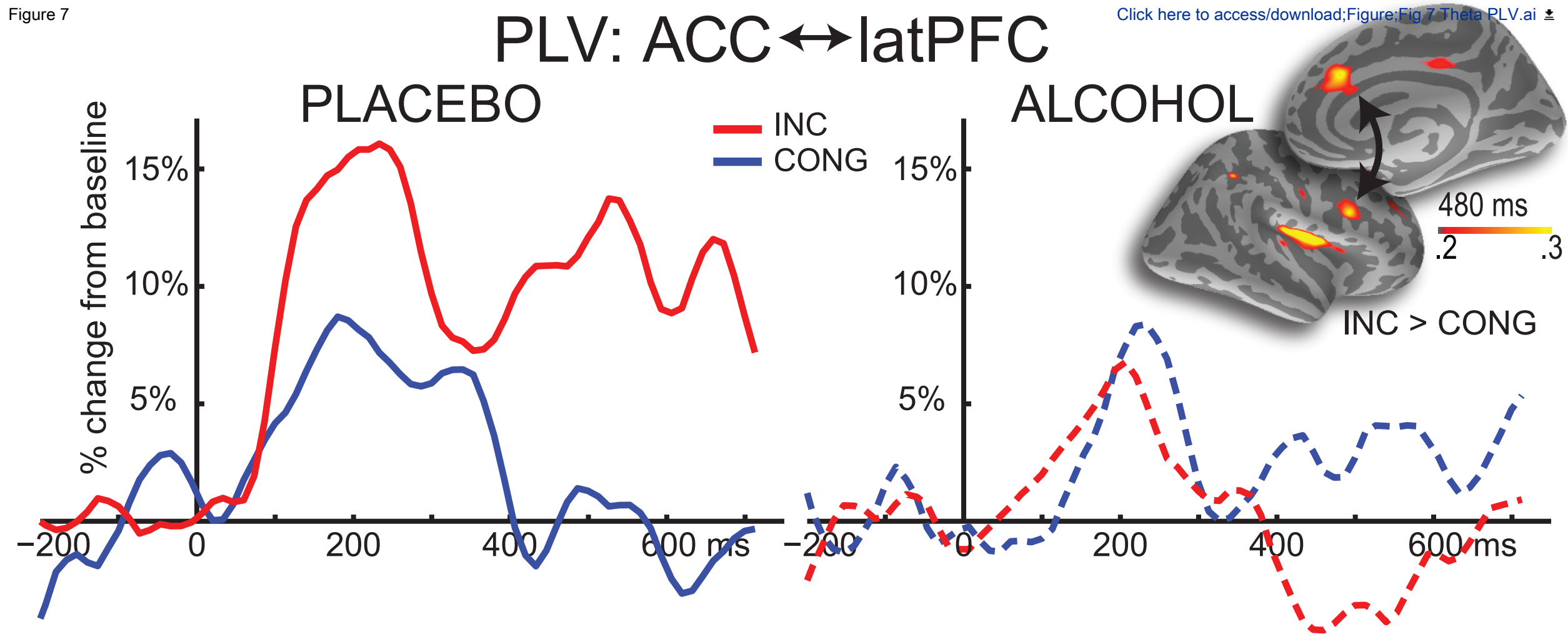


Figure 7



Animated Figure 1

Click here to access/download

Video or Animated Figure

Movie 1 Co-oscillations.mov

Animated Figure 2a

Click here to access/download

Video or Animated Figure

Movie 2a Medial.mp4

Animated Figure 2b

Click here to access/download
Video or Animated Figure
Movie 2b Lateral.mp4

Name of Material/ Equipment	Company
Elekta Neuromag	Elekta
1.5 T GE EXCITE HG	General Electric
Gold Cup Electrodes	OpenBCI
Prep Check Impedance Meter	General Devices
HPI Coils	Elekta
Alcotest	Draeger
Fiber Optic Response Pad	Current Designs, Inc
Grey Goose Vodka	Bacardi
Orange Juice	Naked
Discover Drug Test Card	American Screening C
QED Saliva Alcohol Test	OraSure Technologies
Urine Hcg Test Strips	Joylive
Short Michigan Alcohol Screening Test	Selzer et al., 1975
Zuckerman Sensation Seeking Scale	Zuckerman, 1971
Eysenck Impulsivity Inventory	Eysenck & Eysenck, 19
Eysenck Personality Questionnaire	Eysenck & Eysenck, 19
Biphasic Alcohol Effects Scale	Martin et al., 1993

	Catalog Number	Comments/Description
		Magnetoencephalography system
		Magnetic Resonance Imaging scanner
		Electroencephalography electrodes for o
		Check electrode impedances
		Head position indicator coils for co-regist
		Breathalyzer
		MEG-compatible response pad
		Vodka is used during the alcohol session
		Orange juice is used as the beverage duri
orp		Multi-screen drug test
		Saliva alcohol test
		Pregnancy test
		Alcoholism screening questionnaire
		Questionnaire: disinhibitory, novelty-see
978		Questionnaire: impulsivity traits
975		Questionnaire: personality traits
		Questionnaire: subjective experience of t

ptional simultaneous EEG recording

:ration

ing the placebo session as well as mixed with vodka during the alcohol session

king, and socialization traits

:he effects of alcohol

jove JOURNAL OF VISUALIZED EXPERIMENTS
1 Alewife Center #200
Cambridge, MA 02140
tel. 617.945.9051
www.jove.com

ARTICLE AND VIDEO LICENSE AGREEMENT

Title of Article:	Turning off the executive: Disruption of frontal lobe neural synchrony by alcohol intoxication
Author(s):	Marinkovic K, Beaton L, Rosen BQ, Happer J, Wagner, L

Item 1: The Author elects to have the Materials be made available (as described at http://www.jove.com/publish) via:

[x] Standard Access [ ] Open Access

Item 2: Please select one of the following items:

[x] The Author is **NOT** a United States government employee.

[ ] The Author is a United States government employee and the Materials were prepared in the course of his or her duties as a United States government employee.

[ ] The Author is a United States government employee but the Materials were NOT prepared in the course of his or her duties as a United States government employee.

ARTICLE AND VIDEO LICENSE AGREEMENT

1. **Defined Terms.** As used in this Article and Video License Agreement, the following terms shall have the following meanings: "**Agreement**" means this Article and Video License Agreement; "**Article**" means the article specified on the last page of this Agreement, including any associated materials such as texts, figures, tables, artwork, abstracts, or summaries contained therein; "**Author**" means the author who is a signatory to this Agreement; "**Collective Work**" means a work, such as a periodical issue, anthology or encyclopedia, in which the Materials in their entirety in unmodified form, along with a number of other contributions, constituting separate and independent works in themselves, are assembled into a collective whole; "**CRC License**" means the Creative Commons Attribution-Non Commercial-No Derivs 3.0 Unported Agreement, the terms and conditions of which can be found at: http://creativecommons.org/licenses/by-nc-nd/3.0/legalcode; "**Derivative Work**" means a work based upon the Materials or upon the Materials and other pre-existing works, such as a translation, musical arrangement, dramatization, fictionalization, motion picture version, sound recording, art reproduction, abridgment, condensation, or any other form in which the Materials may be recast, transformed, or adapted; "**Institution**" means the institution, listed on the last page of this Agreement, by which the Author was employed at the time of the creation of the Materials; "**JoVE**" means MyJove Corporation, a Massachusetts corporation and the publisher of The Journal of Visualized Experiments; "**Materials**" means the Article and / or the Video; "**Parties**" means the Author and JoVE; "**Video**" means any video(s) made by the Author, alone or in conjunction with any other parties, or by JoVE or its affiliates or agents, individually or in collaboration with the Author or any other parties, incorporating all or any portion of the Article, and in which the Author may or may not appear.

2. **Background.** The Author, who is the author of the Article, in order to ensure the dissemination and protection of the Article, desires to have the JoVE publish the Article and create and transmit videos based on the Article. In furtherance of such goals, the Parties desire to memorialize in this Agreement the respective rights of each Party in and to the Article and the Video.

3. **Grant of Rights in Article.** In consideration of JoVE agreeing to publish the Article, the Author hereby grants to JoVE, subject to **Sections 4** and **7** below, the exclusive, royalty-free, perpetual (for the full term of copyright in the Article, including any extensions thereto) license (a) to publish, reproduce, distribute, display and store the Article in all forms, formats and media whether now known or hereafter developed (including without limitation in print, digital and electronic form) throughout the world, (b) to translate the Article into other languages, create adaptations, summaries or extracts of the Article or other Derivative Works (including, without limitation, the Video) or Collective Works based on all or any portion of the Article and exercise all of the rights set forth in (a) above in such translations, adaptations, summaries, extracts, Derivative Works or Collective Works and(c) to license others to do any or all of the above. The foregoing rights may be exercised in all media and formats, whether now known or hereafter devised, and include the right to make such modifications as are technically necessary to exercise the rights in other media and formats. If the "Open Access" box has been checked in **Item 1** above, JoVE and the Author hereby grant to the public all such rights in the Article as provided in, but subject to all limitations and requirements set forth in, the CRC License.

4. **Retention of Rights in Article.** Notwithstanding the exclusive license granted to JoVE in **Section 3** above, the Author shall, with respect to the Article, retain the non-exclusive right to use all or part of the Article for the non-commercial purpose of giving lectures, presentations or teaching classes, and to post a copy of the Article on the Institution's website or the Author's personal website, in each case provided that a link to the Article on the JoVE website is provided and notice of JoVE's copyright in the Article is included. All non-copyright intellectual property rights in and to the Article, such as patent rights, shall remain with the Author.

5. **Grant of Rights in Video – Standard Access.** This **Section 5** applies if the "Standard Access" box has been checked in **Item 1** above or if no box has been checked in **Item 1** above. In consideration of JoVE agreeing to produce, display or otherwise assist with the Video, the Author hereby acknowledges and agrees that, Subject to **Section 7** below, JoVE is and shall be the sole and exclusive owner of all rights of any nature, including, without limitation, all copyrights, in and to the Video. To the extent that, by law, the Author is deemed, now or at any time in the future, to have any rights of any nature in or to the Video, the Author hereby disclaims all such rights and transfers all such rights to JoVE.

6. **Grant of Rights in Video – Open Access.** This **Section 6** applies only if the "Open Access" box has been checked in **Item 1** above. In consideration of JoVE agreeing to produce, display or otherwise assist with the Video, the Author hereby grants to JoVE, subject to **Section 7** below, the exclusive, royalty-free, perpetual (for the full term of copyright in the Article, including any extensions thereto) license (a) to publish, reproduce, distribute, display and store the Video in all forms, formats and media whether now known or hereafter developed (including without limitation in print, digital and electronic form) throughout the world, (b) to translate the Video into other languages, create adaptations, summaries or extracts of the Video or other Derivative Works or Collective Works based on all or any portion of the Video and exercise all of the rights set forth in (a) above in such translations, adaptations, summaries, extracts, Derivative Works or Collective Works and (c) to license others to do any or all of the above. The foregoing rights may be exercised in all media and formats, whether now known or hereafter devised, and include the right to make such modifications as are technically necessary to exercise the rights in other media and formats. For any Video to which this **Section 6** is applicable, JoVE and the Author hereby grant to the public all such rights in the Video as provided in, but subject to all limitations and requirements set forth in, the CRC License.

7. **Government Employees.** If the Author is a United States government employee and the Article was prepared in the course of his or her duties as a United States government employee, as indicated in **Item 2** above, and any of the licenses or grants granted by the Author hereunder exceed the scope of the 17 U.S.C. 403, then the rights granted hereunder shall be limited to the maximum rights permitted under such statute. In such case, all provisions contained herein that are not in conflict with such statute shall remain in full force and effect, and all provisions contained herein that do so conflict shall be deemed to be amended so as to provide to JoVE the maximum rights permissible within such statute.

8. **Protection of the Work.** The Author(s) authorize JoVE to take steps in the Author(s) name and on their behalf if JoVE believes some third party could be infringing or might infringe the copyright of either the Author's Article and/or Video.

9. **Likeness, Privacy, Personality.** The Author hereby grants JoVE the right to use the Author's name, voice, likeness, picture, photograph, image, biography and performance in any way, commercial or otherwise, in connection with the Materials and the sale, promotion and distribution thereof. The Author hereby waives any and all rights he or she may have, relating to his or her appearance in the Video or otherwise relating to the Materials, under all applicable privacy, likeness, personality or similar laws.

10. **Author Warranties.** The Author represents and warrants that the Article is original, that it has not been published, that the copyright interest is owned by the Author (or, if more than one author is listed at the beginning of this Agreement, by such authors collectively) and has not been assigned, licensed, or otherwise transferred to any other party. The Author represents and warrants that the author(s) listed at the top of this Agreement are the only authors of the Materials. If more than one author is listed at the top of this Agreement and if any such author has not entered into a separate Article and Video License Agreement with JoVE relating to the Materials, the Author represents and warrants that the Author has been authorized by each of the other such authors to execute this Agreement on his or her behalf and to bind him or her with respect to the terms of this Agreement as if each of them had been a party hereto as an Author. The Author warrants that the use, reproduction, distribution, public or private performance or display, and/or modification of all or any portion of the Materials does not and will not violate, infringe and/or misappropriate the patent, trademark, intellectual property or other rights of any third party. The Author represents and warrants that it has and will continue to comply with all government, institutional and other regulations, including, without limitation all institutional, laboratory, hospital, ethical, human and animal treatment, privacy, and all other rules, regulations, laws, procedures or guidelines, applicable to the Materials, and that all research involving human and animal subjects has been approved by the Author's relevant institutional review board.

11. **JoVE Discretion.** If the Author requests the assistance of JoVE in producing the Video in the Author's facility, the Author shall ensure that the presence of JoVE employees, agents or independent contractors is in accordance with the relevant regulations of the Author's institution. If more than one author is listed at the beginning of this Agreement, JoVE may, in its sole

jove JOURNAL OF VISUALIZED EXPERIMENTS
1 Alewife Center #200
Cambridge, MA 02140
tel. 617.945.9051
www.jove.com

ARTICLE AND VIDEO LICENSE AGREEMENT

discretion, elect not take any action with respect to the Article until such time as it has received complete, executed Article and Video License Agreements from each such author. JoVE reserves the right, in its absolute and sole discretion and without giving any reason therefore, to accept or decline any work submitted to JoVE. JoVE and its employees, agents and independent contractors shall have full, unfettered access to the facilities of the Author or of the Author's institution as necessary to make the Video, whether actually published or not. JoVE has sole discretion as to the method of making and publishing the Materials, including, without limitation, to all decisions regarding editing, lighting, filming, timing of publication, if any, length, quality, content and the like.

12. **Indemnification.** The Author agrees to indemnify JoVE and/or its successors and assigns from and against any and all claims, costs, and expenses, including attorney's fees, arising out of any breach of any warranty or other representations contained herein. The Author further agrees to indemnify and hold harmless JoVE from and against any and all claims, costs, and expenses, including attorney's fees, resulting from the breach by the Author of any representation or warranty contained herein or from allegations or instances of violation of intellectual property rights, damage to the Author's or the Author's institution's facilities, fraud, libel, defamation, research, equipment, experiments, property damage, personal injury, violations of institutional, laboratory, hospital, ethical, human and animal treatment, privacy or other rules, regulations, laws, procedures or guidelines, liabilities and other losses or damages related in any way to the submission of work to JoVE, making of videos by JoVE, or publication in JoVE or elsewhere by JoVE. The Author shall be responsible for, and shall hold JoVE harmless from, damages caused by lack of sterilization, lack of cleanliness or by contamination due to the making of a video by JoVE its employees, agents or independent contractors. All sterilization, cleanliness or decontamination procedures shall be solely the responsibility of the Author and shall be undertaken at the Author's expense. All indemnifications provided herein shall include JoVE's attorney's fees and costs related to said losses or damages. Such indemnification and holding harmless shall include such losses or damages incurred by, or in connection with, acts or omissions of JoVE, its employees, agents or independent contractors.

13. **Fees.** To cover the cost incurred for publication, JoVE must receive payment before production and publication the Materials. Payment is due in 21 days of invoice. Should the Materials not be published due to an editorial or production decision, these funds will be returned to the Author. Withdrawal by the Author of any submitted Materials after final peer review approval will result in a US$1,200 fee to cover pre-production expenses incurred by JoVE. If payment is not received by the completion of filming, production and publication of the Materials will be suspended until payment is received.

14. **Transfer, Governing Law.** This Agreement may be assigned by JoVE and shall inure to the benefits of any of JoVE's successors and assignees. This Agreement shall be governed and construed by the internal laws of the Commonwealth of Massachusetts without giving effect to any conflict of law provision thereunder. This Agreement may be executed in counterparts, each of which shall be deemed an original, but all of which together shall be deemed to me one and the same agreement. A signed copy of this Agreement delivered by facsimile, e-mail or other means of electronic transmission shall be deemed to have the same legal effect as delivery of an original signed copy of this Agreement.

A signed copy of this document must be sent with all new submissions. Only one Agreement is required per submission.

CORRESPONDING AUTHOR

Name:	Ksenija Marinkovic, Ph.D.
Department:	Department of Psychology (SDSU); Department of Radiology (UCSD)
Institution:	San Diego State University; University of California, San Diego
Title:	Associate Professor of Psychology (SDSU), Assoc. Prof. of Radiology (UCSD)
Signature:	
Date:	7-26-2018

Please submit a **signed** and **dated** copy of this license by one of the following three methods:

1. Upload an electronic version on the JoVE submission site
2. Fax the document to +1.866.381.2236
3. Mail the document to JoVE / Attn: JoVE Editorial / 1 Alewife Center #200 / Cambridge, MA 02140

SAN DIEGO STATE UNIVERSITY

SDSU Center for Clinical and Cognitive Neuroscience

Ksenija Marinković, Ph.D.

http://stbil.sdsu.edu/index.html

Associate Professor
Psychology Department
San Diego State University
Spatio-Temporal Brain Imaging Lab
6505 Alvarado Rd. Suite 202, MC-1879
San Diego, CA 92120
tel. (619)594-1510
email: kmarinkovic@mail.sdsu.edu

Center for Clinical
and Cognitive Neuroscience
Core faculty
San Diego State University

Adjunct Associate Professor
Department of Radiology
University of California, San Diego

September 10, 2018

To: Science Editor
Journal of Visual Experiments

Dear Dr. Myers,

We are grateful to you, Dr. Cao, and the reviewers for all the thoughtful and constructive comments and suggestions. We have addressed them here below and have included the corresponding changes in the manuscript which has, we believe, improved significantly. The questions and concerns are listed below point by point in regular font and are followed by replies in *italics*. All modifications in the revised manuscript are visibly marked to facilitate review.

Editorial comments:

2. Please provide an email address for each author.
This information has been added to the manuscript.

3. Please shorten the Long Abstract to 150-300 words.
The Long Abstract has been shortened to the specified length.

4. Please revise the protocol to contain only action items that direct the reader to do something (e.g., "Do this," "Ensure that," etc.). The actions should be described in the imperative tense in complete sentences wherever possible. Avoid usage of phrases such as "could be," "should be," and "would be" throughout the Protocol. Any text that cannot be written in the imperative tense may be added as a "Note." Please include all safety procedures and use of hoods, etc. However, notes should be used sparingly and actions should be described in the imperative tense wherever possible.

The protocol has been revised to the imperative mood with any text that does not fall under these guidelines classified as a "Note".

5. Step 2, etc.: The Protocol should contain only action items that direct the reader to do something. Please move the discussion about the protocol to the Discussion.

Please see above under 4. On several occasions, we have included a brief note to clarify the reason for a particular step or an imperative instruction. For instance, in 3.5.1. we clarify the need to position the participants correctly with the following note: "head position can affect activity estimates in significant ways because the magnetic field gradients decrease with the cube of the distance between the sensors and the brain sources".

6. Please add more details to your protocol steps. There should be enough detail in each step to supplement the actions seen in the video so that viewers can easily replicate the protocol. Please ensure you answer the "how" question, i.e., how is the step performed? Alternatively, add references to published material specifying how to perform the protocol action. Some examples:

Additional detail has been added to the protocol. For the examples below, the new description has been copied below along with the line numbers. Additional changes have been made within the text to clarify each action.

3.1.2: Please describe how to carry out a brief mock recording run and administer the task practice.

> *Carry out an initial recording in the MEG scanner following the protocol described below in sections 3.2, 3.3 and 3.5. Do not provide any beverage. Run the practice version of the task allowing participants to get familiarized with it beforehand.*

3.2.1: How to run a brief test scan? Please specify.

> *Upon their arrival to the MEG lab, run a brief test scan by putting the participant in the scanner and checking the channels for possible magnetization.*

3.4.2: Please specify for how many times BAC is measured.

> *Check the participants' BrAC with the breathalyzer starting at ~15 min after drinking and then every 5 min until they enter the shielded room. Since electronic devices cannot be used in the shielded room, use a saliva alcohol test (Q.E.D., OraSure Technologies), which consists of a q-tip that is saturated in saliva and is inserted into a receptacle that provides a readout.*

3.5.6: What does "the empty room" refer to?

> *When the participant has exited the scanner, acquire approximately two minutes of data from the empty room as a measure of instrumental noise.*

4.3: Please specify how.

> *Use the inner skull surface derived from the segmented structural MRI images to generate a boundary element model of the volume conductor, which is used to provide a model for the forward solution that is consistent with each individual's brain anatomy (Gramfort et al., 2010; Kybic et al., 2005).*

7. 5.1-5.8: Software must have a GUI (graphical user interface) and software steps must be more explicitly explained ('click', 'select', etc.). Please add more specific details (e.g. button clicks for software actions, numerical values for settings, etc.) to your protocol steps. There should be

enough detail in each step to supplement the actions seen in the video so that viewers can easily replicate the protocol.

As suggested, we have included specific functions/commands along with the relevant parameters that need to be run to accomplish such basic processing/analysis tasks, as well as more details on how to visualize results of the various analyses with GUI-based platforms by specifying "clicking" or "selecting" actions.
Please note, however, that the actual analyses carried out by many/most software platforms that handle imaging data at this level of complexity are not run via GUIs but with commands/functions. For example, filtering is accomplished by defining filtering parameters in the filter command itself - no GUI is used for that purpose.

8. Please include single-line spaces between all paragraphs, headings, steps, etc.
These formatting changes have been added.

9. After you have made all the recommended changes to your protocol (listed above), please highlight 2.75 pages or less of the Protocol (including headings and spacing) that identifies the essential steps of the protocol for the video, i.e., the steps that should be visualized to tell the most cohesive story of the Protocol.
10. Please highlight complete sentences (not parts of sentences). Please ensure that the highlighted part of the step includes at least one action that is written in imperative tense.
11. Please include all relevant details that are required to perform the step in the highlighting. For example: If step 2.5 is highlighted for filming and the details of how to perform the step are given in steps 2.5.1 and 2.5.2, then the sub-steps where the details are provided must be highlighted.

The steps appropriate for visualization have now been highlighted.

12. Please obtain explicit copyright permission to reuse any figures from a previous publication. Explicit permission can be expressed in the form of a letter from the editor or a link to the editorial policy that allows re-prints. Please upload this information as a .doc or .docx file to your Editorial Manager account. The Figure must be cited appropriately in the Figure Legend, i.e. "This figure has been modified from [citation]."

Our figures have been modified from our publication in PLoS ONE, which uses the Creative Commons Attribution (CC BY) license. Under this license, authors retain ownership of the copyright for their content, but they allow anyone to download, reuse, reprint, modify, distribute and/or copy the content as long as the original authors and source are cited.

13. Figure 2 legend: Should the unit for 4-7 be Hz instead of H?

Apologies for this inadvertent lapsus calami. Yes, this has been corrected to Hz.

14. Figures 3 and 9: Please include a space between numbers and their corresponding units (i.e., 800 ms, 400 ms).

The suggested change has been made to the figures.

15. Lines 288-289 and 296-297: Please convert the reference to a superscripted numbered reference.

The reference has been converted.

16. Figure 7 legend: Please define error bars in the figure legend. Please define the two treatments “Plac” and “Alc”.

The figure legend has been clarified.

17. Please renumber the videos as movie 1, movie 2, etc. Please number video 8a and 8b as separate movies.

The videos have been renamed to Movie 1 (from figure 5) and Movie 2 (from figure 8). Please note that the two videos previously numbered 8a and 8b are meant to be shown simultaneously to show both the medial and lateral sides of the right hemisphere. They are the same length & timing. We have numbered them as such to suggest that they are part of the same figure. Given this information, if we should still rename them in separate numbers we are happy to do so.

18. JoVE articles are focused on the methods and the protocol, thus the discussion should be similarly focused. Please revise the Discussion to explicitly cover the following in detail in 3-6 paragraphs with citations:
a) Critical steps within the protocol
b) Any modifications and troubleshooting of the technique
c) Any limitations of the technique
d) The significance with respect to existing methods
e) Any future applications of the technique

…
19. References: Please do not abbreviate journal titles.

Reviewers' comments:

We would like to thank all three reviewers for their careful reading of the manuscript and for sharing their expertise as reflected in thoughtful and constructive comments and suggestions.

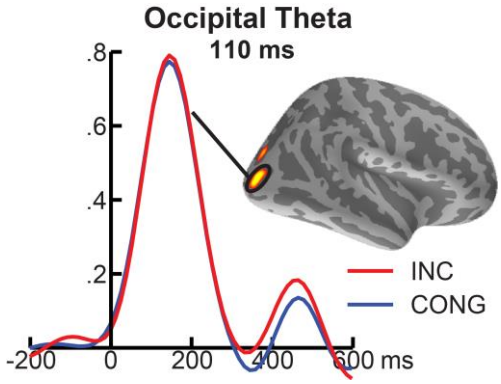
Reviewer #1:

Manuscript Summary:
The MS explores whether the MEG event-related theta oscillations in theta freq band changes the brain dynamics during a higher cognitive demand (i.e. incongruent condition) in two specific regions of brain (ACC and latPFC). The authors conclude that ACC theta oscillatory power increases during incongruent condition about 100 ms in ACC, and about 100-200 ms later in

latPFC. Alcohol condition changes this theta increase during incongruent condition. The authors comment this finding in favor of the effect of alcohol in top-down regulation by means of theta oscillatory responses.

Major Concerns:
1. The visual modality is chosen for the cognitive task, however the changes in primary or association visual cortices were not included to the study. How are the ROI ACC and latPFC was chosen solely? Please provide the rationale for choosing these two areas in more detail.

While the stimulus modality is indeed visual, no differences in theta power estimated to the visual cortex were detected between task conditions, as demonstrated in this figure. Indeed, previous studies from our lab using word stimuli have found no differences in early activation of the visual cortices using time-domain analyses [1-5]. This is due, in part, to carefully balancing stimulus sensory parameters such as word length, size, or color, as the early processing in the visual cortex is not expected to be sensitive to word meaning.



Extensive evidence points to the anterior cingulate cortex (ACC) as a central node in a predominantly frontal cortical network subserving cognitive control [6-10], referring to the capacity to inhibit automatic responses in favor of relevant, but non-habitual responses [11-13]. As described in the introduction, Conflict Monitoring theory [6,7] proposes that the ACC monitors for conflict between competing representations and that it engages latPFC to maintain performance. However, since this account is primarily based on temporally imprecise BOLD-fMRI, the presumed interplay between the medial and lateral prefrontal cortex has not been verified adequately [14]. The anatomically-constrained MEG method described here can test this basic tenet by examining the nature and the extent of the theta oscillatory synchrony between the ACC and latPFC. Indeed, theta oscillations may represent the fundamental mechanism of integrating task-relative information across different cortical domains [15-20]. We hypothesize that increased cognitive demands are associated with greater functional synchrony and that alcohol-induced dysregulation of synchronous activity of the medial and lateral prefrontal cortices underlies impairments of cognitive control.

2. How the authors reached the conclusion that processes start from posterior and extends to anterior? Please explain more explicitly and discuss it with relevant literature.

One of the principle advantages of the aMEG methodology is the ability to observe the spread of cortical activity in time and space. As seen in the "brain movies," (Movie 2a-b), the earliest visual stimulus-locked signal arises in the visual cortex. It is followed by activity that progresses anteriorly toward the supramodal (or sensory-nonspecific) areas in the pre-supplementary motor area, the ACC, and latPFC which is more prominent on incongruous trials. Simultaneous activation of these distributed areas presumably underlies cognitive processing, before the primary motor cortex activation signals the subject's response and the end of the trial. Taken

together this pattern of activation demonstrates an overall posterior-to-anterior sequence of visual processing which is consistent with anatomical, functional, and developmental evidence from animal models [21,22], as well as intracranial EEG in humans [23,24], and MEG recordings [1-5,25-27].

Minor Concerns:
On the page 26 and 27 catalogue numbers are placed out of page margins.
We will ensure that the manuscript is formatted properly.

Reviewer #2:

Manuscript Summary:
The paper describes a protocol to study the effects of alcohol intoxication on oscillatory brain activity in humans using anatomically-constrained MEG. The protocol is useful for characterizing brain networks associated with cognitive control and their sensitivity to pharmacological challenge.

Major Concerns:
None.

Minor Concerns:
The methods are clearly described and motivated. I have the following minor comments:

- line 276: Figure 3 should show axes with appropriate scales for the Morlet wavelet.
We agree with the reviewer that the Figure should describe the Morlet wavelet with appropriate scaling parameters. The new version of the Figure contains the suggested change.

- line 278-281: The caption for Fig. 4 refers to "group averages of theta power" and "sulcal estimates", but those are not shown in the Figure. Please clarify.

The purpose of the figure is to illustrate inflated cortical surface used as an anatomical constraint for MEG source estimates but we agree that the caption may be confusing without activity estimates.
The caption now reads:
Figure 4: Cortical reconstruction and inflation. *Individual cortical surfaces are reconstructed using FreeSurfer and are used to constrain estimated source power. Here shown is an average cortical surface which is inflated to enhance visibility of the sources estimated to cortical sulci.*

- line 287: "arbitrary units" is neither correct nor acceptable. Since these are noise-normalized values, it appears that there are no units.

As the reviewer correctly points out, there are indeed no units associated with noise-normalized values so "arbitrary units" is not uncommon for dimensionless quantities. However, figure captions now describe it as "source power".
We would be glad to consider alternative labels that the reviewer may care to suggest

- line 299: In Fig. 8 (and similarly in Fig. 9) please show the color scale and explain what is the measure shown (and preferably re-format the numbers to 0.72, 0.79, etc.)

We agree with the reviewer that the color scale for these figures should be explained. The new figures and figure legends contain the suggested changes.
Please note that the movies have been streamlined and now show the timing. The color scale is described in the figure caption.

- line 303: The caption says "after ~250" but in the video the activity occurs only at ~350 ms. Please check the consistency of the latencies.

The suggested change has been made.

- line 308: Was zero-lag excluded in the evaluation of the PLV measure? This seems important for reducing spurious connectivity due to the spatial spreading of the estimated source power.

We concur with the reviewer on the importance of considering potential confounds resulting from field spread. Schoffelen and Gross [28] have provided an excellent review of this problem. Their paper includes a simulation of connectivity analysis based on a 248-channel 4D neuroimaging magnetometer system and a realistic head model. However, it is important to note that this particular system seems to use magnetometers which are sensitive to magnetic flux at some distance from the source. In contrast, the largest signal detected by planar gradiometers that were used in the present study (Neuromag Elekta) is above the source as they measure the rate of change in flux between two coils [29,30]. Direct comparisons between the two types of sensors indicate that planar gradiometers have better spatial sensitivity [31] which has been borne out by comparisons based on real data [32].

Ultimately, this is a question of localization uncertainty which is influenced by a variety of factors including the spread of the signal from the generator to the sensors, the limited sampling of the field (even with a very large number of sensors), and the overlap of activity from different sources at each sensor, all within the context of a particular inverse procedure. Liu and colleagues [33] estimated localization uncertainty with the same inverse approach used here [34] and concluded that the values of the estimated point-spread extent average around 20 mm based on the 122 MEG sensor locations and on single-subject solutions. Since the estimated localization accuracy improves with increasing the number of sensors and multiple subjects, it is reasonable to assume that the spatial resolution obtained in the current study is appreciably better.
While zero-lag contributions to PLV were not excluded this study, the inter-ROI distance is certainly greater than 20 mm, mitigating these concerns.

- line 319 (and similarly 361) : "By optimally combining.." It is not clear what is being optimized here. Perhaps the word "optimal" can simply be deleted.

We agree that "optimal" is vague and unquantified in this context and it has been omitted from the text.
The discussion has been expanded and it now summarizes how this methodology combines the complementary features of each technique.

Reviewer #3:

Manuscript Summary:

The authors describe a protocol for anatomically-constrained MEG (aMEG) modelling of functional brain activity during a Stroop task under two within-subject conditions: alcohol and placebo. The purpose of the study is to measure response interference during the task, and how that is altered by alcohol consumption. The main measures of interest were frontal theta (3-7 Hz) power in the anterior cingulate cortex (ACC) and lateral prefrontal cortex (latPFC). In addition, the authors describe a method for measuring co-oscillations in the theta frequency band across these two sources using a Phase-Locking Value (PLV). The authors found increased frontal theta power in both sources for incongruous trials over congruous trials, in both conditions. In addition, the increase in theta power over baseline and PLV were reduced in the alcohol condition. They conclude that these findings support the role of the ACC in monitoring for conflict in processing stages, that intoxicated individuals exhibit deficient self-control, that the aMEG method provides a temporally-sensitive insight into functional brain activity, which can serve as biomarkers of individual vulnerability to pharmacological effects.

Major Concerns:

1. It appears that the time-locked power changes (evoked response) is not subtracted from the raw data prior to computing low frequency theta activity. As a result what is labeled theta power following the stimulus could contain an ERN-like evoked response, originating from the ACC and latPFC.

The reviewer correctly notes that we did not remove the evoked response prior to computing the event-related theta activity. However, it has been demonstrated {Cohen, 2011 #7894} that for conflict-related activity specifically, removing the ERP component does not markedly change the effect size of theta band modulation. More broadly, the practice of subtracting the evoked responses is based on the assumption that the two processes are independent. However, evidence indicates that the stimulus resets the phase and modulates the amplitude of the ongoing oscillations during cognitive processing, suggesting a single underlying process [35 16 36]. This may not hold true, however, for short latency, high frequency responses characteristic of sensory processing, but that was not of primary interest in the current study.

2. There is no mention or description of statistical methods as they apply to the reliability of the results.

We regret this unfortunate omission.
This information has been added to the text and it reads as follows:

5.9.1 Extract time windows of interest from each ROI time course and perform ANOVAs with beverage (alcohol, placebo) and trial type (CONG, INC) as within subject factors. Use a nonparametric cluster-based permutation test [37] to examine beverage and condition comparisons of event-related theta power as well as PLVs.

In addition, results of statistical analyses and their respective significance values have been provided in the representative results section and figure captions, where appropriate.

3. For the Stroop task - how many trials are there and what proportion of trials are congruent?

Details on this particular version have been added to the text: the CONG and INC conditions were equiprobable and were presented on 16.7% trials each out of 576 trials total.

4. What are participants told about this experiment? Are they made aware that one condition is placebo? And is their awareness tested in some way?

The Reviewer raises an important issue concerning alcohol administration and possible effects of expectancies. In a series of studies, we have employed a within-subject design in which participants serve as their own controls. All participants imbibe both alcohol and placebo in a counterbalanced manner so that alcohol is presented in the first session for half the sample and in the second session for the other half. This design controls for neurophysiological idiosyncrasies, resulting in less error variance and has indeed been used in a great majority of neuroimaging studies of acute intoxication [38-46].

Participants are told that in each session they will consume a beverage that may or may not contain a moderate dose of alcohol. The dose is calculated based on each subject's gender and weight to adjust for the body mass index difference [47]. The beverages are administered cold and do not markedly differ in taste given a strong taste of natural orange juice. However, all of our participants have had experience with drinking mixed alcoholic beverages and they all drink regularly in social situations. They are familiar with the timeline of alcohol metabolic process and how it affects them and are able to easily discern the beverage content based on a variety of sensations. At the end of each experimental session the participants are queried about their estimated intoxication levels, beverage contents, and the estimated number of "drinks" contained in the beverage. The results in all of our studies indicate that participants are aware of the beverage content.

The essential question is whether this knowledge (i.e. expectancy) could influence their brain activity. Balanced placebo design makes it theoretically possible to dissociate the pharmacological effects of alcohol from the effects of instructions as to the beverage content by fully crossing the factor of beverage (given alcohol or given placebo) and the factor of instructions, "expectancy" (told alcohol or told placebo). This means that subjects participate in four sessions of the balanced placebo design in a random order. They undergo the same procedure each time except for the consumed beverage and information concerning the alcohol content. In two sessions they are told the correct beverage content (i.e. given and told juice and given and told alcohol). In the other two sessions they are given inaccurate information regarding the beverage content (i.e. given juice/told alcohol and given alcohol/told juice). The beverage administration in all sessions includes the cues (e.g. vodka bottle) appropriate to the instructional expectancy condition procedure [48]. For example, in the given juice/ told alcohol condition, strong olfactory cues are provided by a small piece of vodka-saturated gauze placed in the cap of the bottle with water, unbeknownst to the participants. In an effort to parse out the "expectancy" effects from the pharmacological effects of alcohol, some of our previous studies employed the balanced placebo design in a within-subject setting and with a lower alcohol dose, 0.4 g/kg for men [49-51]. We observed only pharmacological effects of alcohol on physiological and behavioral measures during cognitive tasks. Expectancy did not affect the ERP or autonomic measures in those studies. However, this design has its own problems as it is difficult to

implement all the cells of the balanced placebo design with equal success, even at rather low doses [52-54]. For example, if an alcoholic beverage is given, it is virtually impossible to convince participants that they drank only juice. Crucially, however, even when subjects are successfully tricked into believing that the beverage contains some alcohol, this expectancy has no effect on any of the physiological measures and only the actual administration of (moderately low dose of) alcohol results in observable changes [49-51].

Minor Concerns:

Intro:
-[line 65] "multifaceted role in integrating modulatory effects within a goal-directed context" -> The meaning of this statement is unclear.
-[line 66] Gap in lit: "However, the nature of the involvement of the ACC and the ways it exerts top-down influences on response selection, inhibition, and execution are not clear." This is not clear and rather vague.

These two sentences have been replaced with:

While the abundant anatomical connectivity between the ACC and lateral frontal cortices is well-described [55,56], the functional characteristics of communication between these regions during cognitive control, response selection and execution, are poorly understood.

-[line 76] "slower" -> quantify

It has been well established that the individual postsynaptic currents, which in aggregate form MEG/EEG signal have durations in ms [57] and are, for that reason, sampled at 1000 Hz in this experiment. Within one trial, the entire sequence of cortical activations presented here, from early visual system to motor response, occurs over several hundred ms. In contrast, the hemodynamic response that forms the basis of the BOLD, peaks at 4-6 sec after stimulus onset and, following a post stimulus undershoot, levels approximately 20 sec after stimulus onset [58]. Therefore, the wording has been modified as follows:
As a result, the BOLD signal changes unfold on a much slower time scale (in seconds) than the underlying neural events (in msec) [58].

-[line 104] "to measure…in real time" -> Acquisition is in real time, measurement (i.e. analysis of oscillatory activity and synchrony) are not.

The wording has been changed to "high temporal precision".

Protocol:
-[line 114] how many females?

This information has been added to the text. Eight women and twelve men participated in this experiment.

-[line 115] "no alcohol- or drug-related problems" -> please explain

All potential participants are screened for possible alcohol or drug dependence. The description now reads as follows:
twenty young, healthy individuals (mean ± SD age = 25.3 ± 4.4 years, 8 women) were recruited who drink in moderation, who have never been in treatment or arrested for drug or alcohol related offenses, who report no alcoholism-related symptoms on the Short Michigan Alcoholism Screening Test [59] who do not smoke nor use illegal substances, who do not have a history of neuropsychiatric disorders or any current health problems, who are medication free, and have no internal ferromagnetic objects or implants.

-[line 124] is 1 of these a placebo?

Step 2.1. now clarifies the experimental design as follows:
Scan each participant four times, including three MEG sessions (a no-beverage introductory session and two experimental beverage sessions in which alcohol and placebo are administered in a counterbalanced manner), and one structural MRI scan.

-[line 128] any examples or further descriptions of typical questionnaires?

We thank the reviewer for pointing out this omission.
The description now reads as follows:
During the initial introductory session, administer questionnaires to obtain more information about the participants' medical history, their drinking patterns and severity of alcoholism-related symptoms [60 59], family history of alcoholism [61], and personality traits including impulsivity [62,63].

-[line 143] I suppose these values for food and alcohol deprivation are based on previous work? Ref.

It is known that food influences BrAC as it delays absorption [64]. Therefore, in our studies of acute intoxication we request that participants do not eat 3 hrs prior to the experiment [49 50 51,65 26,66 67 68 69 5,70,71 72].

-[line 145] "multi-drug test panel" - source?

This information has been added to the text as follows:
Collect urine samples for a multi-drug test panel (American Screening, LLC) from all participants and exclude those who test positive for any drug.

-[line 163] This single reference to EEG seems inappropriate

Should the experimenter be interested in collecting simultaneous EEG, this is the step of the protocol during which the experimenter should affix the EEG cap or electrodes to the head.

-[line 165] Note this procedure is specific to Neuromag systems only.

Thank you for pointing this out. It has been noted in the text.

-[line 171] formula for calculating BAC of 0.06%?

This has been clarified as follows in step 3.4.1.:
Prepare alcohol beverage by mixing premium quality vodka with chilled orange juice (25% v/v), based on each participant's gender and weight (0.60 g/kg alcohol for men, 0.55 g/kg alcohol for women), targeting a BrAC of 0.06% [47].

-[line 172] placebo with voka on rim - an estimate of BAC for this condition?

This minuscule amount is not detectable and the BrAC is zero.

-[line 174] breathalyzer source?

The breathalyzer maker (Dräger, Inc.) is now specified in the text in 3.2.1.

-[line 176] saliva alcohol test - description and source?

This information has been added to the text in 3.4.2.: Q.E.D.®, OraSure Technologies

-[line 219] what is the baseline? What is the timing and duration of the event-relate theta power?
Baseline is the period immediately preceding stimulus onset and it serves as a reference to the change in theta power after stimulus onset. Theta power is calculated as event-related theta power and is commonly expressed as percent signal change relative to baseline.
Theta power and duration vary as a function of the stage of processing (shorter during sensory processing, longer during cognitive integration and in more difficult tasks).

-[line 223] Are the ROIs whole-brain?

Regions of Interest (ROIs) are selected based on overall group-averaged estimates to incorporate cortical locations with most notable source power. Figure 5 shows the ACC and latPFC ROIs.

Results:-[line 242] " The ACC is the principal generator of theta oscillations" -> this is not always true, and should be qualified and limited to this particular task

The wording of this sentence, as well as the movie caption has been changed to reflect that the ACC is the principal generator of theta oscillations during tasks evoking cognitive control.

-[line 246] "…especially in the prefrontal cortex." -> Reference?

This statement is now supported by relevant references.
As observed here and in previous reports[17,26,71,72], theta oscillations increase in power in response to cognitive demands such as overriding prepotent or dominant patterns of behavior, which is primarily subserved by prefrontal cortical regions.

-[line 247] How is theta power measured? Using max power? AUC? Also, does the relationship for reduced theta power on incongruent trials in the alcohol condition hold across conditions? (i.e. incongruous_placebo - incongruous_alcohol)?

Data analysis is described in greater detail in step 5. MEG Data Analysis. Morlet wavelets are used to calculate complex power spectrum for each trial in 1 Hz increments within theta frequency band (4-7 Hz).
As described here and in previous reports [26,71], even though acute alcohol intoxication attenuates theta power during cognitive control tasks, the effects are greatest on high conflict (incongruous) trials and in more difficult tasks.

-[line 252] There is no clear null hypothesis here.

In this instance, the null hypothesis would indicate that there is no effect of task congruity or beverage on phase locking values between regions.

-What was done with the questionnaires that were administered?

Questionnaire data can be used to examine correlations with MEG estimates to enrich and facilitate interpretation of the observed effects.
This is now specified in step 5.11.

Discussion:

-[line 326-328] This relationship equally holds for the congruent condition, that there is greater theta power in the prefrontal cortex compared to the prestimulus baseline.

The wording had been changed to reflect increased theta to incongruous trials compared to congruous trials.

-[line 331-332] "… in response preparation and execution" this was not tested or measured in this experiment.

This sentence has been removed from the discussion.

-[line 352] how do the PLV results compare to other studies?

As briefly mentioned in the discussion, the current study extends previous findings indicating that alcohol disrupts synchronized co-oscillations [72,73].

Please note that the reference list is enclosed here below.

On behalf of all the co-authors, I thank you for your consideration.

Sincerely,

Ksenija Marinković, Ph.D.

REFERENCES:

1 Dhond, R. P., Buckner, R. L., Dale, A. M., Marinkovic, K. & Halgren, E. Spatiotemporal maps of brain activity underlying word generation and their modification during repetition priming. *J Neurosci.* **21** (10), 3564-3571, (2001).

2 Dhond, R. P., Marinkovic, K., Dale, A. M., Witzel, T. & Halgren, E. Spatiotemporal maps of past-tense verb inflection. *Neuroimage.* **19** (1), 91-100, (2003).

3 Marinkovic, K. *et al.* Spatiotemporal dynamics of modality-specific and supramodal word processing. *Neuron.* **38** (3), 487-497, (2003).

4 Marinkovic, K. *et al.* Right hemisphere has the last laugh: neural dynamics of joke appreciation. *Cogn Affect Behav Neurosci.* **11** (1), 113-130, (2011).

5 Marinkovic, K., Rosen, B. Q., Cox, B. & Hagler, D. J., Jr. Spatio-temporal processing of words and nonwords: Hemispheric laterality and acute alcohol intoxication. *Brain Res.* **1558** 18-32, (2014).

6 Botvinick, M. M. Conflict monitoring and decision making: reconciling two perspectives on anterior cingulate function. *Cogn Affect Behav Neurosci.* **7** (4), 356-366, (2007).

7 Carter, C. S. & van Veen, V. Anterior cingulate cortex and conflict detection: an update of theory and data. *Cogn Affect Behav Neurosci.* **7** (4), 367-379, (2007).

8 Paus, T. Primate anterior cingulate cortex: where motor control, drive and cognition interface. *Nat Rev Neurosci.* **2** (6), 417-424, (2001).

9 Posner, M. I., Rothbart, M. K., Sheese, B. E. & Tang, Y. The anterior cingulate gyrus and the mechanism of self-regulation. *Cogn Affect Behav Neurosci.* **7** (4), 391-395, (2007).

10 Ridderinkhof, K. R., van den Wildenberg, W. P., Segalowitz, S. J. & Carter, C. S. Neurocognitive mechanisms of cognitive control: the role of prefrontal cortex in action selection, response inhibition, performance monitoring, and reward-based learning. *Brain Cogn.* **56** (2), 129-140, (2004).

11 Procyk, E., Tanaka, Y. L. & Joseph, J. P. Anterior cingulate activity during routine and non-routine sequential behaviors in macaques. *Nat Neurosci.* **3** (5), 502-508, (2000).

12 Roelofs, A., van Turennout, M. & Coles, M. G. Anterior cingulate cortex activity can be independent of response conflict in Stroop-like tasks. *Proc Natl Acad Sci U S A.* **103** (37), 13884-13889, (2006).

13 Raichle, M. E. *et al.* Practice-related changes in human brain functional anatomy during nonmotor learning. *Cereb Cortex.* **4** (1), 8-26., (1994).

14 Gehring, W. J. & Knight, R. T. Prefrontal-cingulate interactions in action monitoring. *Nat Neurosci.* **3** (5), 516-520, (2000).

15 Wang, C., Ulbert, I., Schomer, D. L., Marinkovic, K. & Halgren, E. Responses of human anterior cingulate cortex microdomains to error detection, conflict monitoring, stimulus-response mapping, familiarity, and orienting. *J Neurosci.* **25** (3), 604-613, (2005).
16 Halgren, E. *et al.* Laminar profile of spontaneous and evoked theta: Rhythmic modulation of cortical processing during word integration. *Neuropsychologia.* **76** 108-124, (2015).
17 Cavanagh, J. F. & Frank, M. J. Frontal theta as a mechanism for cognitive control. *Trends Cogn Sci.* **18** (8), 414-421, (2014).
18 Sauseng, P., Griesmayr, B., Freunberger, R. & Klimesch, W. Control mechanisms in working memory: a possible function of EEG theta oscillations. *Neurosci Biobehav Rev.* **34** (7), 1015-1022, (2010).
19 Jacobs, J., Kahana, M. J., Ekstrom, A. D. & Fried, I. Brain oscillations control timing of single-neuron activity in humans. *J Neurosci.* **27** (14), 3839-3844, (2007).
20 Kahana, M. J. The cognitive correlates of human brain oscillations. *J Neurosci.* **26** (6), 1669-1672, (2006).
21 Baker, C. I. in *Handbook of Psychology: Behavioral Neuroscience* Vol. 3 eds R.J. Nelson & S.J.Y. Mizumori) 81-114 (John Wiley & Sons, Inc., 2013).
22 Kravitz, D. J., Saleem, K. S., Baker, C. I., Ungerleider, L. G. & Mishkin, M. The ventral visual pathway: an expanded neural framework for the processing of object quality. *Trends Cogn Sci.* **17** (1), 26-49, (2013).
23 Halgren, E., Baudena, P., Heit, G., Clarke, J. M. & Marinkovic, K. Spatio-temporal stages in face and word processing. I. Depth-recorded potentials in the human occipital, temporal and parietal lobes [corrected] [published erratum appears in J Physiol Paris 1994;88(2):following 151]. *J Physiol Paris.* **88** (1), 1-50, (1994).
24 Klopp, J., Halgren, E., Marinkovic, K. & Nenov, V. Face-selective spectral changes in the human fusiform gyrus. *Clin Neurophysiol.* **110** (4), 676-682, (1999).
25 Marinkovic, K. Spatiotemporal dynamics of word processing in the human cortex. *The Neuroscientist.* **10** (2), 142-152, (2004).
26 Marinkovic, K., Rosen, B. Q., Cox, B. & Kovacevic, S. Event-related theta power during lexical-semantic retrieval and decision conflict is modulated by alcohol intoxication: Anatomically-constrained MEG. *Frontiers in Psychology.* **3** (121), (2012).
27 Marinkovic, K., Courtney, M. G., Witzel, T., Dale, A. M. & Halgren, E. Spatio-temporal dynamics and laterality effects of face inversion, feature presence and configuration, and face outline. *Front Hum Neurosci.* **8** 868, (2014).
28 Schoffelen, J. M. & Gross, J. Source connectivity analysis with MEG and EEG. *Hum Brain Mapp.* **30** (6), 1857-1865, (2009).
29 Hari, R. *et al.* IFCN-endorsed practical guidelines for clinical magnetoencephalography (MEG). *Clin Neurophysiol.* **129** (8), 1720-1747, (2018).
30 Malmivuo, J. & Plonsey, R. *Bioelectromagnetism: Principles and Applications of Bioelectric and Biomagnetic Fields*. (Ozdoes University Press, 1995).
31 Malmivuo, J., Suihko, V. & Eskola, H. Sensitivity distributions of EEG and MEG measurements. *IEEE Trans Biomed Eng.* **44** (3), 196-208, (1997).
32 Irimia, A., Erhart, M. J. & Brown, T. T. Variability of magnetoencephalographic sensor sensitivity measures as a function of age, brain volume and cortical area. *Clin Neurophysiol.* **125** (10), 1973-1984, (2014).
33 Liu, A. K., Dale, A. M. & Belliveau, J. W. Monte Carlo simulation studies of EEG and MEG localization accuracy. *Hum Brain Mapp.* **16** (1), 47-62., (2002).
34 Dale, A. M. *et al.* Dynamic statistical parametric mapping: combining fMRI and MEG for high-resolution imaging of cortical activity. *Neuron.* **26** (1), 55-67, (2000).
35 Makeig, S. *et al.* Dynamic brain sources of visual evoked responses. *Science.* **295** (5555), 690-694, (2002).

36 David, O., Kilner, J. M. & Friston, K. J. Mechanisms of evoked and induced responses in MEG/EEG. *Neuroimage.* **31** (4), 1580-1591, (2006).

37 Maris, E. & Oostenveld, R. Nonparametric statistical testing of EEG- and MEG-data. *J Neurosci Methods.* **164** (1), 177-190, (2007).

38 Bragulat, V. *et al.* Alcohol sensitizes cerebral responses to the odors of alcoholic drinks: an fMRI study. *Alcohol Clin Exp Res.* **32** (7), 1124-1134, (2008).

39 Calhoun, V. D., Pekar, J. J. & Pearlson, G. D. Alcohol intoxication effects on simulated driving: exploring alcohol-dose effects on brain activation using functional MRI. *Neuropsychopharmacology.* **29** (11), 2097-2017, (2004).

40 Calhoun, V. D. *et al.* Alcohol intoxication effects on visual perception: An fMRI study. *Hum Brain Mapp.* **21** (4), 298-299, (2004).

41 Gilman, J. M., Ramchandani, V. A., Davis, M. B., Bjork, J. M. & Hommer, D. W. Why we like to drink: a functional magnetic resonance imaging study of the rewarding and anxiolytic effects of alcohol. *J Neurosci.* **28** (18), 4583-4591, (2008).

42 Meda, S. A. *et al.* Alcohol dose effects on brain circuits during simulated driving: an fMRI study. *Hum Brain Mapp.* **30** (4), 1257-1270, (2009).

43 Paulus, M. P., Tapert, S. F., Pulido, C. & Schuckit, M. A. Alcohol attenuates load-related activation during a working memory task: relation to level of response to alcohol. *Alcohol Clin Exp Res.* **30** (8), 1363-1371, (2006).

44 Ridderinkhof, K. R. *et al.* Alcohol consumption impairs detection of performance errors in mediofrontal cortex. *Science.* **298** (5601), 2209-2211, (2002).

45 Rzepecki-Smith, C. I. *et al.* Disruptions in functional network connectivity during alcohol intoxicated driving. *Alcohol Clin Exp Res.* **34** (3), 479-487.

46 Trim, R. S. *et al.* Acute ethanol effects on brain activation in low- and high-level responders to alcohol. *Alcohol Clin Exp Res.* **34** (7), 1162-1170, (2010).

47 Breslin, F. C., Kapur, B. M., Sobell, M. B. & Cappell, H. Gender and alcohol dosing: a procedure for producing comparable breath alcohol curves for men and women. *Alcohol Clin Exp Res.* **21** (5), 928-930, (1997).

48 Rohsenow, D. J. & Marlatt, G. A. The balanced placebo design: methodological considerations. *Addict Behav.* **6** (2), 107-122, (1981).

49 Marinkovic, K., Halgren, E., Klopp, J. & Maltzman, I. Alcohol effects on movement-related potentials: a measure of impulsivity? *J Stud Alcohol.* **61** (1), 24-31, (2000).

50 Marinkovic, K., Halgren, E. & Maltzman, I. Arousal-related P3a to novel auditory stimuli is abolished by moderately low alcohol dose. *Alcohol and Alcoholism.* **36** (6), 529-539, (2001).

51 Marinkovic, K., Halgren, E. & Maltzman, I. Effects of alcohol on verbal processing: An ERP study. *Alcohol Clin Exp Res.* **28** (3), 415-423, (2004).

52 Hull, J. G. & Bond, C. F., Jr. Social and behavioral consequences of alcohol consumption and expectancy: a meta-analysis. *Psychol Bull.* **99** (3), 347-360, (1986).

53 Knight, L. J., Barbaree, H. E. & Boland, F. J. Alcohol and the balanced-placebo design: the role of experimenter demands in expectancy. *J Abnorm Psychol.* **95** (4), 335-340, (1986).

54 Lyvers, M. F. & Maltzman, I. The balanced placebo design: effects of alcohol and beverage instructions cannot be independently assessed. *Int J Addict.* **26** (9), 963-972, (1991).

55 Barbas, H. Connections underlying the synthesis of cognition, memory, and emotion in primate prefrontal cortices. *Brain Res Bull.* **52** (5), 319-330, (2000).

56 Morecraft, R. J. & Tanji, J. in *Cingulate neurobiology and disease* (ed B. A. Vogt) 114-144 (Oxford University Press, 2009).

57 Kandel, E. R., Schwartz, J. H., Jessell, T. M., Siegelbaum, S. A. & Hudspeth, A. J. *Principles of Neural Science*. (McGraw-Hill, 2013).

58 Buxton, R. B. *Introduction to Functional Magnetic Resonance Imaging*. (Cambridge University Press, New York, NY, 2002).

59 Selzer, M. L., Vinokur, A. & Van Rooijen, L. A self-administered Short Michigan Alcoholism Screening Test (SMAST). *Journal of Studies on Alcohol.* **36** (1), 117-126, (1975).
60 Babor, T., Higgins-Biddle, J. S., Saunders, J. B. & Monteiro, M. G. AUDIT: The Alcohol use disorders identification test: Guidelines for use in primary care. (WHO: World Health Organization, Geneva, Switzerland, 2001).
61 Rice, J. P. *et al.* Comparison of direct interview and family history diagnoses of alcohol dependence. *Alcohol Clin Exp Res.* **19** (4), 1018-1023, (1995).
62 Eysenck, H. J. & Eysenck, S. B. G. *Manual of the Eysenck Personality Questionnaire*. (Hodder & Staughton, 1975).
63 Eysenck, S. B. & Eysenck, H. J. Impulsiveness and venturesomeness: their position in a dimensional system of personality description. *Psychol Rep.* **43** (3 Pt 2), 1247-1255., (1978).
64 Gentry, R. T. Effect of food on the pharmacokinetics of alcohol absorption. *Alcohol Clin Exp Res.* **24** (4), 403-404, (2000).
65 Rickenbacher, E., Greve, D. N., Azma, S., Pfeuffer, J. & Marinkovic, K. Effects of alcohol intoxication and gender on cerebral perfusion: an arterial spin labeling study. *Alcohol.* **45** (8), 725-737, (2011).
66 Kovacevic, S. *et al.* Theta oscillations are sensitive to both early and late conflict processing stages: effects of alcohol intoxication. *PLoS One.* **7** (8), e43957, (2012).
67 Marinkovic, K., Rickenbacher, E. & Azma, S. Effects of Alcohol Intoxication on Response Conflict in a Flanker Task. *J Addict Res Ther.* **Suppl 3**, (2012).
68 Marinkovic, K., Rickenbacher, E., Azma, S. & Artsy, E. Acute alcohol intoxication impairs top-down regulation of Stroop incongruity as revealed by blood oxygen level-dependent functional magnetic resonance imaging. *Hum Brain Mapp.* **33** (2), 319-333, (2012).
69 Marinkovic, K., Rickenbacher, E., Azma, S., Artsy, E. & Lee, A. K. Effects of acute alcohol intoxication on saccadic conflict and error processing. *Psychopharmacology (Berl).* **230** (3), 487-497, (2013).
70 Rosen, B. Q. *et al.* Oscillatory spatial profile of alcohol's effects on the resting state: Anatomically-constrained MEG. *Alcohol.* **48** (2), 89-97, (2014).
71 Rosen, B. Q., Padovan, N. & Marinkovic, K. Alcohol hits you when it is hard: Intoxication, task difficulty, and theta brain oscillations. *Alcohol Clin Exp Res.* **40** (4), 743-752, (2016).
72 Beaton, L. E., Azma, S. & Marinkovic, K. When the brain changes its mind: Oscillatory dynamics of conflict processing and response switching in a flanker task during alcohol challenge. *PLoS One.* **13** (1), e0191200, (2018).
73 Ehlers, C. L., Wills, D. N. & Havstad, J. Ethanol reduces the phase locking of neural activity in human and rodent brain. *Brain Res.* **1450** 67-79, (2012).

Permissions

Click here to access/download;Supplemental File (Figures, Permissions, etc.);PLOS One Open Access Copyright.docx

https://journals.plos.org/plosone/s/licenses-and-copyright