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Acute Alcohol Intoxication Impairs Top-down Regulation of Stroop Incongruity as Revealed by BOLD fMRI

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Abstract

Functional neuroanatomy of executive functions has been delineated in a large number of neuroimaging studies using conflict-inducing tasks. The neural basis of alcohol's effects on cognitive control is poorly understood despite the evidence of impaired ability to evaluate competing demands and to inhibit maladaptive responses. In order to investigate effects of moderate intoxication, healthy social drinkers participated in both alcohol (0.60 g/kg ethanol for men, 0.55 g/kg for women) and placebo conditions while being scanned using blood oxygen level dependent (BOLD) fMRI. A modified 4-color Stroop task combined reading and color naming and used manual responses. Twenty subjects (10 women) were instructed to press a button corresponding to the font color except when a word was written in gray in which case they had to respond to the meaning of the word. Alcohol increased reaction times and a tendency to make more errors on incongruent trials. Behavioral indices of alcohol-induced premature responding correlated with the current drinking levels and impulsivity traits, suggesting an interaction between alcohol effects and personality predispositions. A distributed fronto-parietal cortical network was activated by incongruity. However, moderate alcohol inebriation selectively attenuated anterior cingulate cortex (ACC) activation during both high-conflict trials and erroneous responses, indicating vulnerability of the regulative function subserved by the ACC. By disrupting top-down, strategic processing, alcohol may interfere with goal-directed behavior, resulting in poor self control. The present results support models proposing that alcohol-induced prefrontal impairments diminish inhibitory control and are modulated by dispositional risk factors and levels of alcohol consumption.

Keywords

cognitive control; anterior cingulate; error-related activity

INTRODUCTION

In order to successfully resolve certain conflict-inducing situations, it is necessary to inhibit responses that are normally automatic and habitual, but that cause interference under new constraints. This ability is termed "cognitive control" and is a hallmark of executive functions as we update and adjust to changing contingencies that indicate appropriate and

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safe behavior. One of the most popular tasks used to probe cognitive control is the Stroop Naming Task (Stroop 1935) that manipulates interference by focusing on one feature of the stimuli while ignoring a dominant one. A series of color words are printed in different colors. On the Incongruent trials, the conflict arises when subjects are asked to focus on the font color while ignoring the habitual but irrelevant tendency to read the word. For instance, they are asked to respond "blue" when the word *red* is printed in blue. This conflict between word reading (reflecting an automatic process) and color naming (reflecting a controlled process) results in increased error rates and slower reaction times (MacLeod 1991).

This task has been employed in a large number of imaging studies. Results of meta-analyses of activation patterns evoked by Stroop task suggest that conflict-induced functional activations are subserved by a predominantly frontal cortical network. Main points of convergence across a large number of studies are bilateral dorsal anterior cingulate cortex (ACC), bilateral but left-dominant inferior frontal junction (IFJ) inferior frontal gyrus (IFG), inferior parietal lobule (IPL), and pre-supplementary motor area (pre-SMA) (Laird, et al. 2005; Neumann, et al. 2005). This activation pattern may not be specific to Stroop task since a highly overlapping prefrontal network is activated by a range of cognitive tasks (Duncan and Owen 2000). Nevertheless, ACC, also termed rostral cingulate zone (Ridderinkhof, et al. 2004), holds a central position in that network. It is activated in a variety of tasks as a function of task difficulty, response conflict, novelty, and anticipation (Bush, et al. 2000; Paus 2001). As it is particularly sensitive to tasks in which automatic responses need to be overcome in favor of task-relevant but non-automatic responses, the ACC seems to underlie controlled processing in a sense of guiding behavior that is not well rehearsed or habitual (Procyk, et al. 2000; Raichle, et al. 1994). This multifaceted top-down role of the ACC in goal-oriented actions is supported by its anatomical connections with dorsolateral prefrontal cortex (dlPFC), motor cortex, spinal cord, and limbic structures (Barbas 2000; Bush, et al. 2000; Devinsky, et al. 1995). Furthermore, fMRI studies indicate its importance in error monitoring and behavioral adjustments (Carter, et al. 1998; Ullsperger and von Cramon 2004). The temporal dimension of error-related responses has been investigated with event-related potentials (ERP). The error-related negativity (ERN) component, presumably generated in the ACC, is evoked on erroneous trials (Coles, et al. 1995; Holroyd and Coles 2002). This deflection is attenuated by alcohol (Easdon, et al. 2005; Holroyd and Yeung 2003; Ridderinkhof, et al. 2002), suggesting vulnerability of the error-monitoring network to alcohol intoxication.

Neuroimaging data delineating alcohol effects on cognitive control are scant in spite of the crucial importance of understanding the neural basis of alcohol's effects on behavioral self-regulation. Gundersen and colleagues (2008) observed decreased activation in ACC and cerebellum during a working memory task under a moderate alcohol dose. A slightly lower alcohol dose and a different variant of a working memory task resulted in increased activation in dlPFC and decreased activation in parietal regions (Paulus, et al. 2006). Impairments in a distributed, but primarily frontal circuitry were observed under conditions of simulated driving while intoxicated (Calhoun, et al. 2004; Meda, et al. 2009). Using Stroop task and event-related potentials, Curtin and Fairchild (2003) reported reduced frontal components to incongruity under alcohol, suggesting impairment in evaluative and regulative processes.

Neuroimaging studies of abstinent chronic alcoholics have observed decreased frontal activation during cognitive control tasks. In a PET study, mediofrontal hypometabolism correlated with response speed on Stroop task in abstinent alcoholics (Dao-Castellana, et al. 1998). Hypoactivity of dlPFC areas was also observed in a cohort of chronic alcoholics with fMRI during a stop-signal task, suggesting impaired impulse control (Li, et al. 2009). These results are in agreement with other lines of research suggesting that chronic alcoholism

results in deficits in executive functions (Oscar-Berman and Marinkovic 2007), with prefrontal cortex being particularly vulnerable to alcohol-induced damage (Sullivan and Pfefferbaum 2005). It has been proposed that the prefrontal deficits underlie inability to control drinking (Kalivas 2009), which is one of the criteria for alcohol dependence (DSM-IV, APA 1994).

It is generally accepted that a decreased ability to inhibit pre-potent responses in favor of the rewarded ones relates to the inability to refrain from drinking and may be a factor in subsequent alcohol or drug abuse (Fillmore 2003; Finn 2000; Jentsch and Taylor 1999; Lyvers 2000). Moreover, impaired cognitive control is influenced by genetics and it contributes to the vulnerability to alcoholism (Schuckit 2009). In spite of their relevance, the effects of acute intoxication on the neural basis of cognitive control are poorly understood. We employed fMRI to investigate alcohol effects on cognitive control as reflected in the ability to inhibit pre-potent responses in favor of the rewarded ones. We used a modified version of the Stroop task that combined color-naming and reading and that contained trials that were high in conflict (i.e. incongruous), low in conflict (i.e. congruous), or neutral (i.e. non-color words). Healthy, young social drinkers served as their own controls by participating in both moderate alcohol and placebo conditions in a counterbalanced manner. We investigated beverage-related impairments in patterns of behavioral and neural activity as a function of task-induced conflict. In addition, we examined effects of inebriation on error-related activity with particular emphasis on the anterior cingulate contributions, given previous reports of attenuated ERN under alcohol (Ridderinkhof, et al. 2002) and the assumed ACC generators (Ullsperger and von Cramon 2001). Taking advantage of the excellent spatial resolution of the fMRI method, we tested the hypothesis of an alcohol-specific decrease in ACC activity on high conflict and erroneous trials. Gender is an important factor mediating alcohol's effects on cognitive control (Fillmore and Weafer 2004). Higher prevalence of alcohol use disorders among men may result from a confluence of genetic, biological, and social factors (Nolen-Hoeksema and Hilt 2006), calling for more research to delineate their respective influences. Consequently, potential gender differences in alcohol's effects on the behavioral and physiological variables were explored in the current study.

METHODS

Research Participants

Twenty individuals (10 women) participated in both alcohol and placebo sessions in a counterbalanced manner. Average age (± st. dev.) was 24.9 ± 3.6 yrs and age range was 21 – 35 yrs. They were all right-handed, non-smoking native English speakers with no alcohol- or drug-related problems. None of the participants had any health-related problems and none were taking any medications. The participants were predominantly white but the sample included one Pacific Islander and two Hispanic individuals. On average, participants reported light-to-moderate drinking pattern imbibing 1.8 ± 1.2 times per week on average, 2.5 ± 1.0 drinks per occasion. Men and women did not differ in the amount or frequency of drinking. No alcoholism-related symptoms were detected with the Short Michigan Alcoholism Screening Test, SMAST (Selzer, et al. 1975) and the subjects reported no family history of alcoholism or drug abuse (first and second degree relatives). Their responses on personality questionnaires were in the normal range.

Task

A modified Stroop paradigm combined trials of reading and color naming in a randomized manner. It consisted of four conditions that varied interference between font color and word meaning (Fig 1). Responses were given manually on a four-button response box. Response

conflict was elicited by the *incongruent* (INC) condition (e.g. word "red" printed in blue color), in comparison to *congruent* (CONG) trials on which the meaning corresponds to the display (e.g. word "red" printed in red color). The *neutral* (NEUT) condition consisted of common non-color words (e.g. word "paid" written in color) that were matched with the color words in length and lexical frequency (Francis and Kucera 1982). Words in the INC, CONG, and NEUT conditions were written equiprobably in four colors (red, green, yellow, blue) and represented 55.5% (18.5% each) of all the trials. Subjects had to respond to the font color of these words. An additional "*reading*" (READ) control condition (on 44.5% trials) consisted of color words written in gray to which subjects pressed the button corresponding to the meaning of the word. The purpose of this condition was to maintain reading dominance and automaticity (Repovs 2004). Subjects were instructed to press a button corresponding to the font color whenever they saw a word written in color and to press a button corresponding to the word meaning when it was written in gray. They were asked to respond on each trial as quickly as possible without losing accuracy while using index and middle fingers of both hands on a four-button magnet-compatible response box. They practiced response mapping with a series of progressively realistic practice runs during a familiarization session. At first they practiced responding to strings of x's written in each color, followed by responding to words written in gray. Finally, they were given a practice run resembling the real experiment and a test run to ascertain that their performance was at perfect or near-perfect levels, i.e. at or above 95% accuracy. Performance accuracy and speed were analyzed with a mixed model ANOVA with gender as a between-group factor and beverage and conditions as within-subject factors (Woodward, et al. 1990), Fig 2. In addition to the F-values and probability, Cohen's d statistic (Cohen 1988) corrected for sample size bias resulting in Hedges' d (Hedges and Olkin 1985) is reported for all mean value comparisons in the text and Tables 1 and 2.

The words were presented for 300 ms on the black background followed by a fixation string (a series of x's) with a total trial length of 2 seconds. The stimuli were shown in the center of a rear-projection presentation screen in a manner synchronized with the scanner using the Presentation software package (Neurobehavioral Systems). Each subject was presented with five 5-min runs that comprised a total of 100 incongruent, 100 congruent, 100 neutral and 240 reading trials. In addition, 190 fixation trials were randomly intermixed providing the temporal jitter needed for optimal deconvolution of the BOLD signal (Burock, et al. 1998). Optimized randomization of the event-related sequence was achieved with the Optseq program within the FS-FAST software (http://surfer.nmr.mgh.harvard.edu/optseq).

Experimental Design and Procedure

Subjects served as their own controls by participating in both alcohol and placebo sessions in a counterbalanced manner. During an introductory session, subjects were familiarized with the laboratory setting, experimental procedure and the task, minimizing potential effects of situation-induced arousal. Subjects also provided more detailed information about their medical history, family history of alcoholism, level of response to alcohol (Schuckit, et al. 1997), severity of their alcoholism-related symptoms (Selzer 1971), quantity and frequency of alcohol use (Cahalan, et al. 1969), and handedness (Oldfield 1971). In order to obtain a comprehensive dispositional profile for each subject particularly with respect to disinhibitory, novelty seeking and socialization traits, the following questionnaires were used: Childhood Hyperactivity Questionnaire, (Tarter, et al. 1977); Eysenck Personality Questionnaire, EPQ (Eysenck and Eysenck 1975); Socialization Scale of the California Psychological Inventory (Gough 1994); Zuckerman Sensation Seeking Scale (Zuckerman 1971); Eysenck Impulsiveness and Venturesomeness Scale (Eysenck and Eysenck 1978). Correlations between scores on personality questionnaires and performance measures were calculated as a function of beverage and described below.

Written informed consent approved by the Human Research Committee at Massachusetts General Hospital and the Partners Healthcare Network was obtained from all subjects before participation. Subsequently, the subjects participated in placebo and alcohol sessions that were counterbalanced in order of presentation. Alcohol was given in the first session to 10 out of 20 subjects. The two sessions were 30 ± 26 days apart on average. Upon their arrival to the laboratory, the subjects were queried about their compliance with the requirement to abstain from food for 3 hours and from alcohol at least 48 hours prior to each experimental session. Female subjects were given a pregnancy test each time to ascertain that they were not pregnant. Blood alcohol concentration (BAC) was measured with a breathalyzer (Draeger, Inc.) upon arrival and throughout the session when the subjects were outside the scanner. During the actual scan we used Q.E.D. Saliva Alcohol Test (OraSure Techn, Inc.) to estimate the BAC since no electronic device can be used in the scanner chamber. Identical procedure was used in both alcohol and placebo sessions with the exception of the beverage contents. The subjects rated their moods and feelings with the adapted Biphasic Alcohol Effects Scale (BAES, Martin, et al. 1993) on three occasions: prior to drinking, on the ascending BAC limb (immediately prior to task performance), and on the descending limb (immediately after the scan). They were asked to rate their momentary feelings on a series of adjectives probing stimulant (e.g. vigorous) and sedative (e.g. sluggish) alcohol effects, as well as how tired, worn-out, high, euphoric, or sexy they felt at the time. The scores on BAES scale were analyzed with a mixed model ANOVA with gender as a between-group factor and beverage (alcohol, placebo) and phase (before experiment, ascending BAC, descending BAC) as within-subject factors on each sub-scale separately.

In each session, either alcohol (0.60 g/kg for men, 0.55 g/kg for women, presented as cocktail containing vodka (Grey Goose, Bacardi) as 20% v/v in orange juice), or placebo (the same volume of orange juice) were administered within a single-blind procedure (Marinkovic, et al. 2004) and consumed in about 10 min. Gender-specific dosing was used in order to adjust for the body mass index difference (Breslin, et al. 1997). On average, participants consumed approximately 2.8 standard drinks defined as 1.5 fl oz of vodka. The task was administered 44 ± 9 min after the subjects were presented with their drink. The average BAC measured before the task was 0.043% ± 0.01% and reached 0.052% ± 0.01% upon its completion, indicating that the task was administered on the ascending BAC limb. It was followed by another task. At the end of each experimental session, the participants filled out a detailed questionnaire about perceived task difficulty, type and content of the beverage they imbibed, about how intoxicated, nauseous or dizzy they felt. Transportation home was provided to all participants upon completion of each session.

Image Acquisition and Analysis

Imaging data were acquired with a 3 T Siemens Trio whole-body scanner (Siemens, Erlangen, Germany). Special care was taken to minimize head motion with the use of a special pillow, foam padding and head “clamps” that also allowed subjects to maintain a comfortable position during scanning. Exposure to scanner noise was reduced with 29 db earplugs and pillow padding. Subjects could view the stimuli comfortably as they were rear-projected onto a mirror fitted onto the head coil. For each subject two high-resolution 3D MPRAGE (magnetization-prepared rapid gradient echo) T1-weighted sequences that optimize contrast for a range of tissue properties were obtained with the following parameters: TR = 2.53 sec, TE = 3.25 msec, flip angle = 7^0, FOV = 256, 128 sagittal slices, 1.33 mm thickness, in-plane resolution 1 × 1 mm. These two high-resolution structural images were used for spatial normalization and cortical surface reconstruction. A series of functional whole-brain BOLD images was collected using a T2*-weighted EPI sequence of 28 interleaved 5mm thick slices in axial-oblique AC-PC orientation with TR = 2 sec, TE =

30 msec, flip angle = 90^0, FOV = 200mm, matrix = 64 × 64, resulting in 3.13 × 3.13 in-plane resolution.

The FreeSurfer and FS-FAST (Free-Surfer – Functional Analysis Stream) analysis package was used to analyze brain images (Burock and Dale 2000; Dale, et al. 1999; Fischl, et al. 1999a). Each subject's cortical surface was reconstructed using an automatic gray/white segmentation, tessellation and inflation of the folded surface patterns (http://surfer.nmr.mgh.harvard.edu/). These surfaces were registered with a canonical brain surface created from an average of 40 brains (Fischl, et al. 1999b) allowing for high-resolution group averaging based on surface alignment. Functional data were motion corrected with AFNI software (Cox 1996; Cox and Jesmanowicz 1999), spatially smoothed with a 3D 5-mm Gaussian full-width half-maximum filter, corrected for temporal drift and normalized to correct for signal intensity changes. The data were carefully checked for motion or artifacts. Motion for one subject's run in one session was 3.25 mm and was excluded, along with the matching run in the complementary session for the same subject. Otherwise, the motion did not exceed 2 mm for any subject or run and did not differ between sessions. Event-related hemodynamic responses (HDR) were estimated with a finite impulse-response model (FIR) (Burock and Dale 2000) which provides unbiased estimates of the average signal intensity at each time point for each trial type and makes no *a priori* assumptions about the shape of the HDR. In order to capture the timecourse of the BOLD activation, the mean and variance values of the HDR were estimated for each TR within a time window of 18 sec. Motion parameters derived from realignment correction were entered into the model as regressors. F-distributed statistical activation maps were generated from averaged responses for each contrast of interest and were resampled onto the common cortical surface space for the surface-based analysis which included trials with correct responses. Contrasts were generated for each condition vs. fixation in order to assess the overall activity whereas conflict -specific activity was examined by contrasting INC vs. other conditions. Group average results were obtained using a random-effects statistical model which takes into account the inter-subject variance, allowing for inferences to the population (Friston, et al. 1999), and projected onto an inflated brain with average curvature (Fischl, et al. 1999b). Potential baseline shifts were removed by subtracting the average hemodynamic response prior to stimulus onset from the hemodynamic response waveform for both "placebo" and "alcohol" conditions, equating their respective baselines. The resulting statistical parametric maps of the voxel-wise group-average analysis are presented in Figures 3 (for the overall activity) and 4 (for the conflict-specific activity). In addition, region-of-interest (ROI) analyses were conducted in order to further explore the main effects and interactions of the factors of gender, beverage, and condition. The ROIs were based on functional features and were defined on a group-average voxel-wise analysis using the unbiased orthogonal contrast (i.e. all contrasts vs. fixation) (Friston, et al. 2006; Poldrack 2007). ROIs included voxels active at $p < 0.0001$ at the activity peak (TR window 4–6 sec latency). The ROI placement was blind to each subject's activation patterns since the group-average based ROIs were automatically transferred from the average cortical surface onto each individual's surface. Percent signal change from baseline was computed for each ROI and each subject, session and condition and presented in the form of timecourses that were also baseline normalized. The ROIs and group-average timecourses for alcohol and placebo are presented in Fig 5. ANOVA analyses were conducted on these values using a mixed model with a between-group factor of gender and within-subject factors of beverage and condition. The reported significance values have been modified to reflect Huynh-Feldt adjustment for the Condition factor since it contains 4 levels. One male subject's data were unusable in one condition because he fell asleep in the scanner so the neuroimaging results are reported for N=19 (10 females).

Error Analysis

In order to explore error-related activity, trials with erroneous responses were matched with correct trials that belonged to the same stimulus type. Half of the matched correct trials preceded and half followed error trials but were never ordinally adjacent as they were separated by intervening trials. The FIR estimates were obtained as described above and group averages were calculated with random-effects statistical model. Results of the voxel-wise analysis at 4–6 sec latency are shown in Fig 6, left panel, for the medial surface of the left and right hemispheres. As described above, ROIs were obtained based on the group-average data and automatically transferred on each subject's cortical surface. Baseline-normalized % signal change values for the factors of Error (error vs. correct) and Beverage (alcohol vs placebo) were entered into a within-subject ANOVA (Fig 6, right panel).

Nine subjects (3 males) that were included in the analysis made 26.2 ± 17.1 errors on average, with the minimum of 15. Possible differences between the participants who did or did not have sufficient number of errors were carefully examined on the scales of task difficulty, intoxication, moods, personality, and BAC. Subjects who were included in the "error" analysis rated the task as being more difficult under intoxication on the Likert 1–5 scale (3.4 ± 0.6), than the participants who made fewer errors (2.5 ± 0.7), $F_{(1,18)} = 12.6$, $p < 0.01$, $d = 1.27$. On the BAES scale, the participants generating more errors reported being less stimulated on the ascending BAC limb (21.9 ± 14.1) than the individuals with fewer errors (33.9 ± 11.5), $F_{(1,18)} = 4.4$, $p < 0.05$, $d = 0.83$. No other differences were detected as the groups did not differ in terms of self-reported intoxication, sedation, BAC, drinking habits, or on any personality measures. These results suggest that increased error rates are not due to inherent personality traits, but may result from situational variations in task difficulty and alcohol-induced moods.

Post-error behavioral adjustment is commonly reflected in slower RTs following incorrect responses (Jentzsch and Dudschig 2009; Rabbitt 2002). In order to examine this phenomenon, the RT analysis included all error trials that were closely followed by a correct response that was strictly matched for the condition type. The errors and post-error correct responses were 4.9 ± 1.1 sec apart. The post-error correct responses were further matched with correct responses belonging to the same condition that were close to the error trial but were, on average, 13.0 ± 2.2 sec apart. Reaction times were analyzed with repeated measures ANOVA including within-subject factors of Beverage (alcohol and placebo) and Trial Type (errors, post-error correct and other correct trials).

RESULTS

Behavioral Measures

Performance—Our task successfully manipulated the Stroop interference effect as indicated by lower accuracy ($F_{1,18} = 24.5$, $p < 0.0001$, $d = 0.82$) and slower RTs ($F_{1,18} = 205.5$, $p < 0.0001$, $d = 1.18$) on incongruent trials as compared to all other conditions (Fig 2). Table 1 lists behavioral results for all beverage comparisons. With the exception of a tendency to make more errors on incongruent trials under alcohol compared to placebo ($F_{1,18} = 3.8$, $p < 0.07$, $d = 0.46$), there were no other beverage or gender effects on performance accuracy. In contrast, RTs were significantly longer under alcohol (762.6 ± 99.6 msec) than under placebo (739.7 ± 96.7 msec) as indicated by the main effect of beverage ($F_{1,18} = 5.6$, $p < 0.05$, $d = 0.23$). Furthermore, the main effect of condition ($F_{3,54} = 125$, $p < 0.0001$) was due to the overall fastest responses on congruent trials, 694.0 ± 80.2 msec ($F_{1,18} = 208$, $p < 0.0001$, $d = 0.76$) and slowest responses on incongruent trials, 840.0 ± 91.8 msec, ($F_{1,18} = 205.5$, $p < 0.0001$, $d = 1.18$), as compared to other conditions. RTs on neutral and read trials did not differ (732.5 ± 71.9 msec; 738.2 ± 86.7 msec respectively) but

were longer than the congruous ($F_{1,18}$ = 64.2, p < 0.0001, d = 0.50) and shorter than the incongruous ($F_{1,18}$ = 148.8, p < 0.0001, d = 1.06) across both beverage conditions.

Mood ratings—There were no gender effects on any of the measures. Overall, subjects felt more sedated and less stimulated at the end of the scan, as indicated by the main effect of Phase for both Stimulation ($F_{2,36}$ = 22.3, p < 0.0001) and Sedation ($F_{2,36}$ = 22.5, p < 0.0001) subscales. Subjects tended to rate themselves as more stimulated on the ascending BAC under intoxication ($F_{1,18}$ = 3.5, p < 0.08, d = 0.33) and were more sedated on the descending BAC ($F_{1,18}$ = 16.6, p < 0.001, d = 0.59) as compared to placebo. This was confirmed with additional mood probes as subjects reported to be significantly more high ($F_{1,18}$ = 12.0, p < 0.01, d = 0.66) and euphoric ($F_{1,18}$ = 6.2, p < 0.05, d = 0.37) and tended to feel more sexy ($F_{1,18}$ = 3.8, p < 0.07, d = 0.15) on the ascending BAC when given alcohol, as compared to placebo. Conversely, they felt significantly more tired ($F_{1,18}$ = 9.1, p < 0.01, d = 0.39) on the descending BAC when comparing alcoholic vs. placebo beverage conditions.

Post-experimental questionnaire—Subjects provided ratings on Likert scales (1–5). Each scale was analyzed with a mixed model ANOVA with gender as a between-group and beverage as a within-subject factor. Participants rated the task as being moderately difficult (2.9 ± 0.7) but the perceived difficulty was not affected by the beverage. On the scale from 1 (definitely contains no alcohol) to 5 (definitely contains alcohol), participants rated the beverage contents as 4.5 ± 0.9 under alcohol and 1.4 ± 0.9 under placebo and these ratings differed significantly ($F_{1,18}$ = 57.0, p < 0.0001, d = 1.66). They estimated that the alcoholic beverage contained 2.3 ± 0.9 “alcoholic drinks” which was a slight underestimate of the actual amount containing 2.8 standard drinks on average defined as 1.5 fl oz of vodka. They also reported that the placebo beverage contained 0.1 ± 0.4 “alcoholic drinks”. No gender effects were found on any of these measures. However, there was a significant interaction between the factors of gender and beverage ($F_{1,18}$ = 4.6, p < 0.05) for the intoxication self-reports. Based on 1–5 Likert scale, women felt more intoxicated than men when given alcohol ($F_{1,18}$ = 4.8, p < 0.05, d = 0.72), as they reported being “moderately intoxicated” (3.2 ± 0.8) whereas men were only “slightly intoxicated” (2.4 ± 0.8). Even though being intoxicated did not affect the nausea ratings on the scale of 1 (not at all) to 5 (very much), (overall rating was 1.2 ± 0.4), subjects reported feeling slightly but significantly dizzier under alcohol (1.9 ± 1.1) as compared to placebo conditions (1.2 ± 0.4), ($F_{1,18}$ = 11.4, p < 0.01, d = 0.81).

Personality questionnaires—Beverage-related differences in the number of self-corrections (trials on which participants corrected themselves) correlated with two measures of impulsivity: Psychoticism Scale of Eysenck’s Personality Questionnaire (r = 0.76, p < 0.001) and Impulsivity Scale on Eysenck’s Impulsiveness and Venturesomeness Scale (r = 0.54, p < 0.01), possibly suggesting that as the baseline impulsivity increases, alcohol causes more impairment in the ability to inhibit the prepotent but erroneous responses.

Neuroimaging Results

Task-induced activity—Voxel-wise analysis was performed using random effects model of the group data. Fig 3 shows the overall activity to all four stimulus types during placebo and alcohol conditions. Conflict-evoked activity (i.e. INC vs. other stimulus types) is presented in Fig 4, indicating a subset of areas that contribute to interference-related activity. For the ROIs representing main foci of cortical activity, additional statistical analyses were performed on activity levels as reflected in baseline-normalized percent signal change values. A distributed cortical network was activated by this interference task, in agreement with results from other fMRI studies using Stroop paradigm summarized with meta analyses

(Laird, et al. 2005; Neumann, et al. 2005). Significant effects are listed in Table 2 and a subset of timecourses is shown in Fig 5.

The most prominent effect of alcohol on baseline-normalized percent signal change measured in ROIs was attenuation of conflict-related activity on the INC trials in ACC regions (Table 2). Activity to INC under placebo was significantly stronger than activity under alcohol both in the left ($F_{1,17} = 4.7$, $p < 0.05$, $d = 0.63$), and right ACC ($F_{1,17} = 8.2$, $p < 0.01$, $d = 0.56$). The main effect of beverage was statistically significant in the right ACC, ($F_{1,17} = 4.6$, $p < 0.05$), with stronger activity under placebo than alcohol (0.11 vs. 0.08 % signal change). This alcohol-induced attenuation of activity on conflict trials was limited to ACC bilaterally. The Main effect of Condition was observed in distributed, but primarily fronto-parietal areas with significantly stronger activity to INC than to other stimulus conditions (Table 2). CONG, NEUT, and READ did not differ in evoked signal strength with one exception. Activity in the left IFG showed graded responses to the four conditions so that the activity to INC was larger than to NEUT, ($F_{1,17} = 9.9$, $p < 0.01$, $d = 0.68$), which, in turn, was larger than activity to CONG, ($F_{1,17} = 14.1$, $p < 0.01$, $d = 0.54$). Activity to CONG was only marginally stronger than the activity to READ, ($F_{1,17} = 2.0$, $p < 0.06$, $d = 0.25$), Fig 5. As discussed below, this unique pattern may be due to the lexico-semantic function ascribed to this area (Wagner, et al. 2001). Effects of gender were limited to the left ACC where men showed stronger overall activity than women ($F_{1,17} = 10.5$, $p < 0.01$, $d = 0.91$).

Error-related activity—Repeated measures ANOVA was carried out on RTs as a function of beverage and correct vs. error responses. Average RTs of the trials included in the imaging analysis were not significantly affected by beverage and did not differ between the errors (798.6 ± 91.9) and correct responses (804.1 ± 96.9).

In order to test the hypothesis of alcohol effects on the neural basis of error processing, the activity generated on error and matched correct trials was analyzed in ACC bilaterally. Fig 6 shows voxel-wise analysis for both alcohol and placebo conditions, as well as average % signal change differences for the ROIs in ACC. The ROI analysis (Fig 6, right panel) indicates that the ACC activity is significantly stronger on error as compared to correct trials, but only under placebo ($F_{1,8} = 6.0$, $p < 0.05$, $d = 0.72$) and not alcohol, ($F_{1,8} = 0.2$, $p > 0.5$, $d = 0.18$). Thus, moderate alcohol inebriation attenuates both conflict-related and error-related activity in ACC area.

Comparison of RTs on the subset of correct trials that closely followed erroneous responses and were matched by condition type with RTs on other matched correct trials and errors indeed confirmed post-error slowing. Beverage did not affect RTs significantly on the three trials types (i.e. error, post-error correct and other correct). Whereas erroneous RTs (829.4 ± 168.7) did not differ from either post-error corrects or other correct responses, the post-error correct responses (819.3 ± 120.0) were indeed significantly longer than other correct responses (760.0 ± 77.2), $F_{(1,8)} = 6.4$, $p < 0.05$, $d = 0.56$, confirming other reports of post-error slowing (Jentzsch and Dudschig 2009; Rabbitt 2002).

DISCUSSION

Our study indicates that a distributed, fronto-parietal cortical network is activated by incongruity during the Stroop task, confirming other reports (Laird, et al. 2005; Neumann, et al. 2005). More importantly, however, activity in the anterior midcingulate area is selectively attenuated by moderate alcohol inebriation during both high conflict trials and erroneous responses. This finding indicates that the regulative, top-down function subserved by the ACC is vulnerable to moderate intoxication (Ridderinkhof, et al. 2002). The

importance of the ACC for cognitive control has been emphasized in a large number of studies showing that it contributes to better performance by maintaining decision contingency in the active attentional focus, by inhibiting inappropriate response tendencies, or by performance monitoring (Bush, et al. 2000; Rushworth, et al. 2004). The ACC may subserve the top-down regulation necessary to maintain performance in high-conflict situations in which prepotent responses need to be overcome in favor of non-automatic, but task-relevant responses (Procyk, et al. 2000; Roelofs, et al. 2006). An appropriate level of cognitive control ensures that our actions are in agreement with our intents and goals, and that they fit with the context. It also includes suitable planning and self-regulation which are necessary to avoid succumbing to distractions, and permits refraining from temptations such as heavy drinking. In contrast to automatic processing that is strongly influenced by the external stimuli, controlled processing comprises effort to overcome habitual responses and perform less practiced tasks (Schneider and Chein 2003). Alcohol disrupts the top-down, strategic mode of processing that is regulated by prior goals and intentions and makes us more susceptible to the momentary and immediate cues. Indeed, it is generally accepted that impaired self-regulation of executive functions such as an inability to refrain from drinking may be a factor in subsequent alcohol or drug abuse (Fillmore 2003; Finn 2000; Lyvers 2000).

Top-down regulative role of the ACC

ACC's executive role is supported by its extensive anatomical connections across different levels of the neuraxis, allowing it to integrate top-down modulatory effects within a goal-directed context. It receives sensory input, has extensive and reciprocal connections with lateral prefrontal cortex and striatum, dense projections to the motor cortex and spinal cord, and its activity is modulated by multiple neurotransmitter systems (Barbas 2000; Devinsky, et al. 1995; Paus 2001; Picard and Strick 2001). Human intracranial EEG studies confirm the multiplicity of the ACC contributions. Very similar inhibitory activity has been observed in the same ACC microdomain as a function of difficulty, rarity, repetition, and errors, indicating its top-down function in regulating and implementing plans to act (Wang, et al. 2005). This finding is consistent with the proposal that ACC enhances signal relevance by exerting inhibitory influence on dlPFC, permitting goal specific stimulus processing (Medalla and Barbas 2009).

ACC lesions result in a variety of impairments including suppression of reflexive saccades (Paus, et al. 1991), deficits in focused attention and initiation of action (Cohen, et al. 1999), increased errors and impaired error correction (Alexander, et al. 2007; Swick and Turken 2002), and deficient assessment of outcomes (Kennerley, et al. 2006). By blunting the ACC activity, alcohol intoxication may partially emulate these effects, rendering a person less able to focus attention, suppress reflexive responding to irrelevant stimuli, monitor performance or initiate purposeful behavior. In this experiment we administered a moderate alcohol dose that people commonly consume to feel a pleasant "buzz" (Chen, et al. 2004/2005). Indeed, participants reported feeling more stimulated, high, euphoric, and sexy on the ascending BAC limb, just before performing the task. Even though alcohol intoxication blunted the ACC activity to both conflict trials and errors and resulted in increased RTs and a tendency to make errors on conflict trials, post-error slowing indicating post-error adjustment did not appear to be affected.

Impaired cognitive control and impulsivity

In the present study, participants were able to marshal greater strategic control and maintain low error rates under placebo. This was reflected in stronger ACC activity under the INC condition. ACC activity was also increased on those trials on which participants made errors, indicating proficient performance monitoring. Conversely, intoxication weakened

top-down regulation on conflict trials as reflected in blunted ACC activation and a tendency to make more errors on INC condition. Alcohol also attenuated error-related ACC activity, suggesting impaired performance monitoring. In addition to a tendency to make more errors to INC stimuli, intoxication resulted in longer response times overall, concurring with other similar observations (Curtin and Fairchild 2003; Rose and Duka 2008). This behavioral pattern is suggestive of a partial accuracy-speed tradeoff. Indeed, correlations between accuracy and RTs under alcohol for the two potentially conflicting conditions, CONG, and INC, were −0.48 and −0.51 respectively, both $p < 0.05$. Post-error slowing observed in this study is consistent with other evidence (Jentzsch and Dudschig 2009; Rabbitt 2002). However, there were no beverage effects on post-error RTs, suggesting that post-error adjustments are not affected by this level of acute intoxication.

Alcohol-induced tendency to make more errors has been suggested to indicate impulsive responding as alcohol impairs the ability to inhibit the prepotent responses that are no longer correct (Fillmore 2003). The present study provides further evidence that impulsivity may result from lowered strategic control as two indices of impulsivity (Psychoticism Scale of Eysenck's Personality Questionnaire and Impulsivity Scale on Eysenck's Impulsiveness and Venturesomeness Scale) correlated with beverage-related differences in the number of self-corrections (trials on which participants corrected themselves). In other words, the participants with higher impulsivity scores made premature responses based on incomplete processing when intoxicated, confirming other similar reports (Marinkovic, et al. 2000). Furthermore, the number of self-corrected responses correlated with current drinking ($r = 0.46$, $p < 0.05$), and also with the Self-Rating of Effects of Alcohol (SRE) reports on the number of drinks required to feel intoxicated when the person first started drinking ($r = 0.53$, $p < 0.01$), suggesting an interaction between the personality predispositions and alcohol effects. Beverage-related differences in RTs also correlated with the current level of drinking ($r = −0.60$, $p < 0.01$), indicating that faster RTs under intoxication were related to higher regular drinking levels.

Impulsivity is a complex construct but it is often operationalized with tasks measuring cognitive control of responses. In a series of studies using a cued go/no-go task, Fillmore and colleagues have found a dose-related increase in commission errors and slower response times to the no-go signals that were falsely preceded by a "go" cue (Marczinski and Fillmore 2003; Marczinski and Fillmore 2005). Similarly, alcohol intoxication decreases cognitive control on the stop-signal task (de Wit, et al. 2000; Mulvihill, et al. 1997), and on a continuous performance task (Dougherty, et al. 1999). Alcohol-induced impairment is reflected in premature motor preparation based on incomplete stimulus evaluation (Marinkovic, et al. 2000). Furthermore, these effects are correlated with personality traits related to impulsivity and hyperactivity (Dougherty, et al. 1999; Marinkovic, et al. 2000). In a broader sense, the underlying symptom concerns an inability to resist engaging in the activity which one declares to be unwanted or even harmful, thus the inability to maintain inhibitory control over drinking has been considered to be fundamental to alcohol abuse (Fillmore 2003; Finn 2000; Jentsch and Taylor 1999; Lyvers 2000). A cluster of traits termed "antisocial personality disorder", inclusive of impulsivity, hyperactivity and sensation/novelty seeking, correlates with the early-onset of alcoholism and increased drinking (Brown, et al. 1996; Finn, et al. 2000; Mazas, et al. 2000), as well as chronic alcohol use and dependence (Hesselbrock, et al. 1985). Vulnerability to alcoholism shares a common genetic component with antisocial personality disorder which, as a premorbid trait, may predispose individuals to a spectrum of conduct disorders including alcohol dependence (Begleiter and Porjesz 1999; Bowirrat and Oscar-Berman 2005; Schuckit 2009). Thus, by impairing top-down regulative functions, alcohol intoxication affects cognitive evaluation of the situation and impairs finding the most suitable response strategies. It may result in disinhibited behaviors, poor-self control and inability to desist drinking leading to a further

increase in alcohol intake and tolerance. Consequently, impulsivity may mediate alcohol abuse both as a dispositional risk factor and as a consequence of excessive drinking.

Cognitive control is subserved by a distributed network

In addition to the ACC, conflict-induced activation was observed in a distributed fronto-parietal network in the present study, with the INC condition evoking stronger activity than all other conditions (Table 2). The other three conditions, CONG, NEUT, and READ, were differentially activated only in the left IFG. Notably, the NEUT condition evoked a stronger activity than CONG, which tended to evoke stronger activation than READ. This area's role in semantic retrieval (Wagner, et al. 2001) explains its activation to NEUT (non-color related) words, in addition to selecting among competing alternatives (Thompson-Schill, et al. 1997). Conflict-related activity was also observed in IFJ, a region which may contribute to cognitive control by setting and updating stimulus-response representations (Brass, et al. 2005; Derrfuss, et al. 2005). It has also been suggested that IFJ is essential for response inhibition (Swick, et al. 2008) and action observation (Binkofski and Buccino 2006). Its function is closely related to the intraparietal cortex (IPC) which is a part of the top-down network that is activated by allocation of attention (Corbetta 1998). It is thought that IPC biases processing and motor planning toward the task-relevant attribute (Wojciulik and Kanwisher 1999) while SMA participates in motor preparation and planning especially for ambiguous tasks (Rushworth, et al. 2004). Insula has been implicated in selective attention (Corbetta, et al. 1991) and working memory (Paulesu, et al. 1993). Even though all of these areas are sensitive to incongruity, only the ACC was affected by alcohol intoxication. This finding suggests that this level of intoxication primarily impairs the top-down central executive centered in ACC, rather than the perceptual or motor output systems.

Conclusions and Limitations

Better insight into the anatomical and functional properties of the ACC is essential for understanding the nature of alcohol-induced impairments, especially in the context of efforts to develop effective pharmacological treatments by targeting the relevant circuits (Myrick and Anton 2004) and gene-neurotransmitter interactions in alcohol dependence (Bowirrat and Oscar-Berman 2005; Schuckit 2009). The results of the present study indicate that moderate alcohol intoxication selectively attenuates ACC activation during high-conflict and error trials, suggesting that the regulative, top-down function is most vulnerable to the effects of alcohol intoxication. ACC is essential in guiding unrehearsed behavior, when new contingencies have to be observed and inappropriate behavior inhibited. By decreasing ACC response to conflict-inducing situations, acute intoxication decreases this self-regulatory influence on behavior, making it potentially more difficult to refrain from drinking and diminishing sound judgment. Furthermore, impulsive and erroneous responding increased under intoxication and was correlated with the current drinking levels as well as impulsivity traits. The present results support models proposing that alcohol-induced prefrontal impairments may result in diminished inhibitory control of impulsive behaviors such as alcohol abuse (Fillmore 2003; Finn 2000; Jentsch and Taylor 1999; Lyvers 2000).

In the present study, effects of gender were limited to only two findings: women reported feeling more intoxicated than men and their ACC activity was lower overall than in men. While this observation may suggest that gender plays a minimal role in the effects of alcohol intoxication on behavioral or physiological measures, future neuroimaging studies with larger samples are needed to explore this question further (Fillmore and Weafer 2004). In addition, potential effects of expectancy need to be explored in future studies.

Alcohol's potentially vasoactive properties need to be considered, however, in interpreting this study's findings. The BOLD effect is expressed relative to baseline and is sensitive to

local changes in cerebral blood flow (CBF), volume (CBV), and metabolic rate of oxygen ($CMRO_2$) (Buxton, et al. 2004). By altering hemodynamics, pharmacological agents such as alcohol may confound interpretation of the neural activation (Tracey 2001). Some animal studies suggest that moderately high alcohol doses do not affect CBF, $CMRO_2$, and glucose metabolism (Ligeti, et al. 1991). However, correct interpretation of effects of alcohol on BOLD signal requires direct measures of CBF in humans, which can be obtained non-invasively with arterial spin labeling (ASL) (Golay, et al. 2004; Liu and Brown 2007). In a different experiment we measured perfusion with ASL technique with the same alcohol dose as used in the present study and found no significant changes in resting CBF (Rickenbacher, et al. 2010). Nevertheless, in order to partially mitigate potential alcohol-induced baseline shifts in this study, alcohol and placebo conditions were equated at baselines by subtracting the average hemodynamic response prior to stimulus onset from the hemodynamic response waveforms. Future ASL studies are needed to investigate potential dose-related effects of alcohol intoxication on cerebral perfusion and BOLD contrast in order to disambiguate potential vascular confounds from neural activity (Brown, et al. 2007; Liu, et al. 2004).

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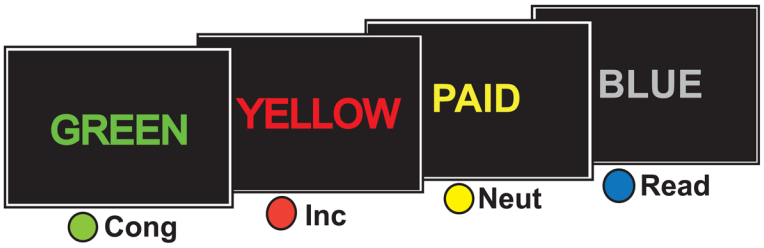

Figure 1.

Trial examples of the four conditions in this modified Stroop paradigm, along with the correct response color for each trial. The task included the Congruent (Cong) condition in which the font color coincides with the word meaning, Incongruent (Inc) condition that elicits response conflict due to incongruity between the font color and the word meaning, and Neutral (Neut) condition in which common words were written in color. Participants were asked to press a button corresponding to the color of the font whenever a word was written in color. Words in the Read condition were written in gray and participants had to press a button corresponding to the word meaning. Trials were presented for 300ms every 2 sec in a randomized manner.

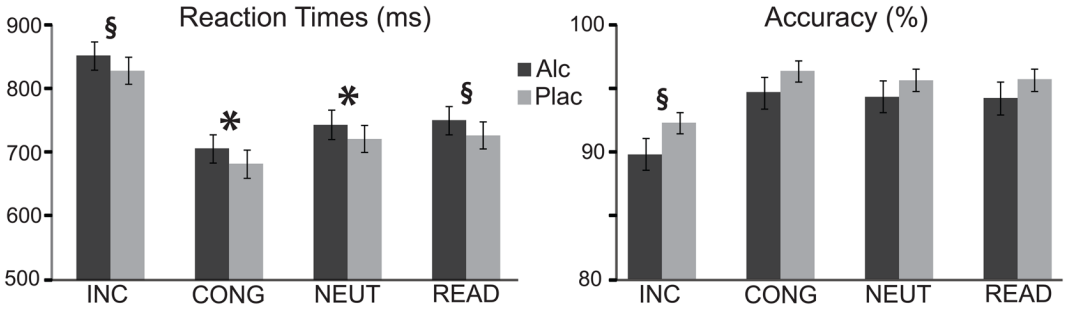

Figure 2.

Stroop color-word interference effect is reflected in longer RTs and lower accuracy on INC trials as compared to other conditions overall. When intoxicated, participants had longer average RTs and tended to make more errors on INC trials. Alcohol vs. placebo comparisons: * $p < 0.05$, § $p < 0.07$.

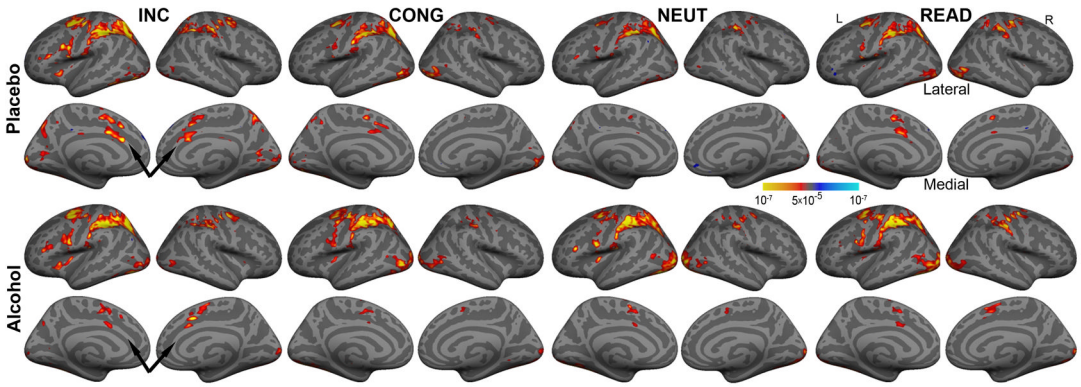

Figure 3.

Voxel-wise group average statistical maps are displayed on the inflated lateral and medial cortical surfaces for both hemispheres and for all conditions under placebo and alcohol at the activity peak (4–6 sec latency). The ACC activity evoked under placebo was significantly attenuated by alcohol (black arrows). The color bar denotes *p*-values obtained with the random effects group analysis of all conditions vs. fixation contrasts.

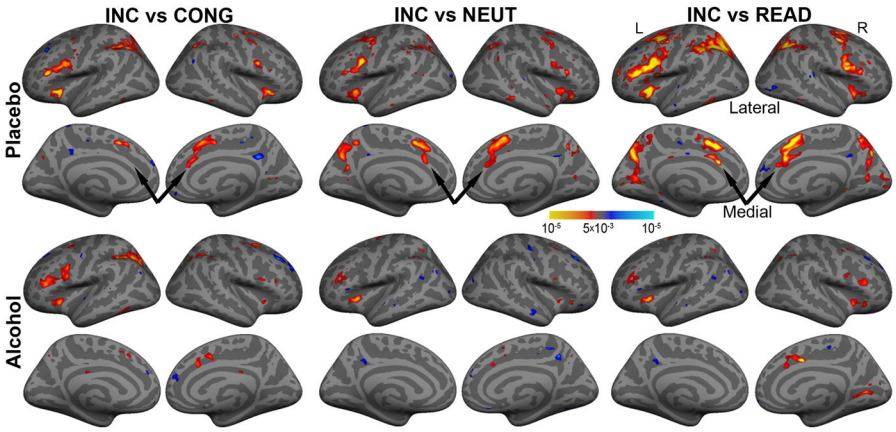

Figure 4.

Voxel-wise group average maps obtained with the random effects group analysis for INC vs. all other conditions contrasts and displayed on the inflated lateral and medial cortical surfaces for both hemispheres and beverage conditions at 4–6 sec latency. Conflict-evoked activity observed in the ACC was stronger under placebo (black arrows) than alcohol.

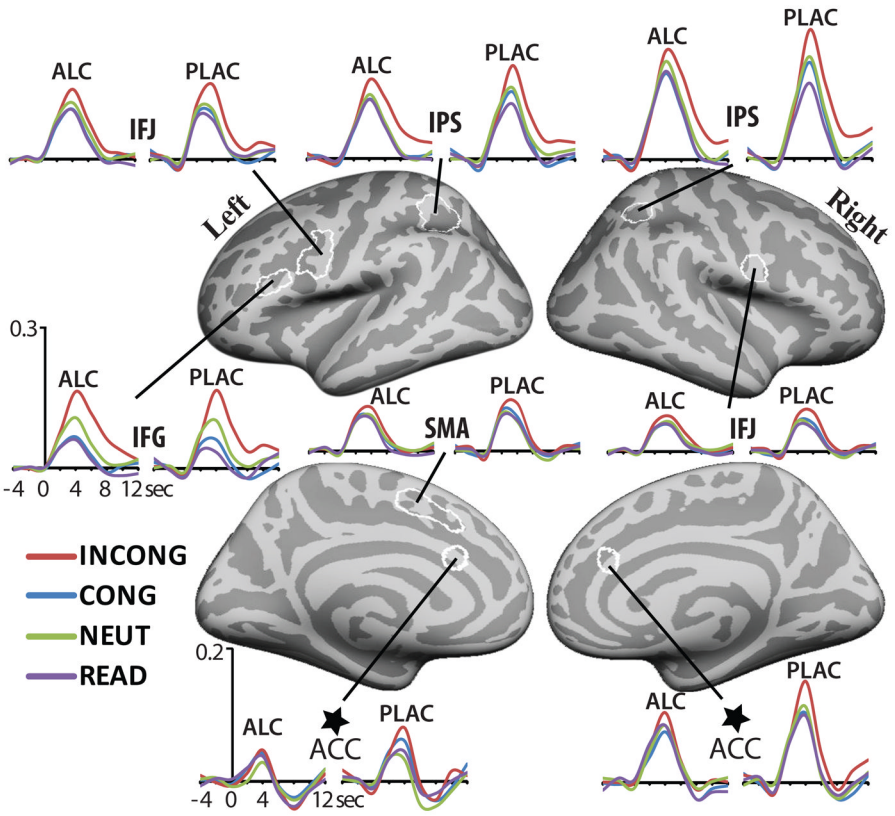

Figure 5.

Shown are group-average timecourses (% signal change) of the BOLD activation for all conditions and both beverages for a set of ROIs. The ROIs (delineated in white) were derived from group-average voxel-wise analysis using the unbiased orthogonal contrast and were baseline normalized. Conflict-related activity was attenuated significantly in the ACC. IFJ: inferior frontal junction; IFG: inferior frontal gyrus; IPS: intraparietal sulcus; SMA: supplementary motor area; ACC: anterior cingulate cortex.

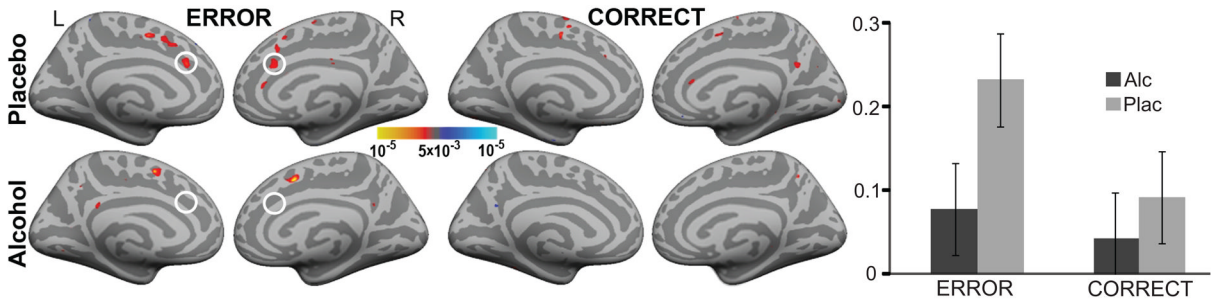

Figure 6.

Group-average voxel-wise random effects analysis of erroneous and correct trials vs. fixation. Significant activity was observed only on medial views of the inflated cortical surfaces as shown in the left figure panel. Right panel: average % signal change (± s.e.m.) from baseline for the bilateral ROIs centered on the ACC, showing that error-induced activity is significantly attenuated under intoxication.

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Table 1

Summary of beverage effects on behavioral measures as reflected in group means ± standard deviations for Placebo and Alcohol conditions, F- and p-values of the difference and Hedges' unbiased d effect size index. Included are measures of performance (accuracy and RTs) for each condition separately as well as average across conditions (All cond); BAES scales (Stimulant, Sedative effects and self-reports on High, Euphoric, Sexy, and Tired scales for the Baseline (before experiment), Ascending and Descending BAC; post-experimental self-reports on Likert scales (1–5) for task difficulty, nausea, dizziness, beverage content and intoxication. Participants also estimated how many alcoholic drinks were contained in the beverage on a scale ranging from 0 to drinks with 0.5 drinks increments. Finally, BAC measures are also included.

			Placebo	Alcohol	$F_{(1,18)}$	p-value	d-value
Performance	**Accuracy**	Inc	92.2 ± 4.9	89.8 ± 5.4	3.8	< 0.07	0.46
		Cong	96.3 ± 2.8	94.6 ± 5.2	1.6	< 0.22	0.39
		Neut	95.6 ± 3.4	94.3 ± 6.3	0.8	< 0.39	0.25
		Read	95.6 ± 2.5	94.2 ± 4.8	2	< 0.17	0.36
		All cond	94.9 ± 3.8	93.2 ± 5.7	2.52	< 0.13	0.35
	RTs	Inc	828.6 ± 86.8	851.3 ± 97.5	3.6	< 0.07	0.24
		Cong	682.3 ± 80.6	705.7 ± 80.1	5.4	< 0.05	0.29
		Neut	721.2 ± 72.1	743.9 ± 71.8	4.5	< 0.05	0.31
		Read	726.8 ± 85.3	749.7 ± 88.9	3.8	< 0.07	0.26
		All cond	739.7 ± 96.7	762.6 ± 99.6	5.6	< 0.05	0.23
BAES Scales	**Stim**	Baseline	24.8 ± 13.6	26.3 ± 13.6	0.24	> 0.5	0.11
		Asc BAC	23.8 ± 14.3	28.5 ± 13.8	3.5	< 0.08	0.33
		Desc BAC	17.8 ± 12.1	16.1 ± 13.8	1	< 0.3	0.13
	Sedat	Baseline	15.5 ± 12.1	15.0 ± 9.8	0.1	> 0.5	0.05
		Asc BAC	14.8 ± 11.3	17.6 ± 11.9	1.7	< 0.2	0.23
		Desc BAC	22.9 ± 14.7	31.5 ± 12.9	16.6	< 0.001	0.59
	High Euph. Sexy Tired	Asc BAC	1.5 ± 2.1	3.2 ± 2.7	12	< 0.01	0.66
		Asc BAC	2.1 ± 2.1	3.05 ± 2.9	6.2	< 0.05	0.37
		Asc BAC	2.3 ± 2.5	2.7 ± 3.0	3.8	< 0.07	0.15
		Desc BAC	4.7 ± 2.5	5.7 ± 2.7	9.1	< 0.01	0.39
Post-Exp.	**Likert 1–5**	Task diff.	3 ± 0.8	2.9 ± 0.8	0.14	> 0.5	0.06
		Nausea	1.2 ± 0.5	1.2 ± 0.4	0.0	> 0.5	0.00

		Placebo	Alcohol	$F_{(1,18)}$	p-value	d-value
	Dizziness	1.2 ± 0.4	1.9 ± 1.1	11.4	< 0.01	0.81
	Bev. cont.	1.4 ± 0.9	4.5 ± 0.9	57.1	< 0.0001	1.66
	Intox.	1.1 ± 0.2	2.8 ± 0.9	70.2	< 0.0001	1.57
scale 0–5	# drinks	0.1 ± 0.4	2.3 ± 0.9	64.2	< 0.0001	1.63
BAC	Before task	0.0 ± 0.0	0.043 ± 0.01	n/a	n/a	n/a
	After task	0.0 ± 0.0	0.052 ± 0.01	n/a	n/a	n/a

Table 2

Summary of statistical results for ROIs including their Talairach coordinates, significance of the main effect of Condition, and comparisons of INC vs all other conditions for alcohol and placebo. Included are F- and p-values of the difference and Hedges' unbiased d effect size index

Area	Talairach coord	Condit. ($F_{3,51}$)	INC- Alc, $F_{1,17}$	d	INC- Plac, $F_{1,17}$	d
left IFG	−42.9 20.7 17.0	26.9 < 0.0001	16.4 < 0.001	0.97	34.1 < 0.0001	1.08
left IFJ	−52.1 3.5 28.1	18.7 < 0.0001	15.3 < 0.001	0.78	30.7 < 0.0001	0.97
left IPC	−29.3 −45.9 45.1	16.4 < 0.0001	23.6 < 0.0001	0.69	23.5 < 0.0001	1.10
left sup PF	−20.9 1.5 44.2	12.1 < 0.0001	21.6 < 0.001	0.39	19 < 0.001	0.74
left aINS	−9.9 4.7 45.1	24.2 < 0.0001	32.5 < 0.0001	0.99	47.4 < 0.0001	1.06
left ACC	−6.2 24.1 21.8	3.8 < 0.01	ns	0.16	14.9 < 0.01 *	0.72
left SMA	−9.0 12.6 42.5	11.8 < 0.0001	7.4 < 0.01	0.42	28.3 < 0.0001	0.54
right IFJ	58.6 5.5 20.5	7.8 < 0.001	8.5 < 0.01	0.35	21.5 < 0.001	0.71
right IPC	27.8 −47.1 43.3	16.1 < 0.0001	9.5 < 0.01	0.41	21.4 < 0.001	0.76
right aINS	31.7 18.6 −1.7	10.1 < 0.0001	10.8 < 0.01	0.59	31.3 < 0.0001	0.78
right ACC	9.3 30.3 18.6	4.7 < 0.01	6.7 < 0.01	0.35	8.1 < 0.01 *	0.58
right SMA	8.9 25.5 39.6	5.5 < 0.01	8.7 < 0.01	0.13	17.4 < 0.001	0.47

* the only ROIs with significant alcohol-induced attenuation of the activity to INC were in the left ACC ($F_{1,17} = 4.7$, $p < 0.05$, $d = 0.63$) and right ACC ($F_{1,17} = 8.2$, $p < 0.01$, $d = 0.56$).

IFG: inferior frontal gyrus; IFJ: inferior frontal junction; IPS: intraparietal sulcus; sup PF: superior prefrontal cortex; aINS: anterior insula; ACC: anterior cingulate cortex; SMA: supplementary motor area