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Alcohol-induced impairment of inhibitory control is linked to attenuated brain responses in right fronto-temporal cortex

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Abstract

Background—A self-enhancing loop between impaired inhibitory control under alcohol and alcohol consumption has been proposed as a possible mechanism underlying dysfunctional drinking in susceptible people. However, the neural underpinnings of alcohol-induced impairment of inhibitory control are widely unknown.

Methods—We measured inhibitory control in fifty young adults with a stop-signal task (SST) during functional magnetic resonance imaging (fMRI). In a single-blind placebo-controlled cross-over design, all participants performed the SST once under alcohol with a breath alcohol concentration (BrAC) of 0.6 g/kg, and once under placebo. In addition, alcohol consumption was assessed using a free-access alcohol self-administration (ASA) paradigm in the same participants.

Results—Inhibitory control was robustly decreased under alcohol compared to placebo indicated by longer stop-signal reaction times (SSRTs). On the neural level, impaired inhibitory control under alcohol was associated with attenuated brain responses in the right fronto-temporal portion of the inhibition network that supports the attentional capture of infrequent stop-signals, and subsequent updating of action plans from response execution to inhibition. Furthermore, the extent of alcohol-induced impairment of inhibitory control predicted free-access alcohol consumption.

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Conclusion—We suggest that during inhibitory control alcohol affects cognitive processes preceding actual motor inhibition. Under alcohol, decreased brain responses in right fronto-temporal areas might slow down the attentional capture of infrequent stop-signals and subsequent updating of action plans which leads to impaired inhibitory control. In turn, pronounced alcohol-induced impairment of inhibitory control may enhance alcohol consumption in young adults which might promote future alcohol problems.

Keywords

response inhibition; inhibitory control; stop-signal task; acute alcohol intoxication; fMRI; alcohol consumption

Introduction

Under the influence of alcohol, individuals are more likely to engage in risky behaviors such as risky driving (e.g., 1; 2), gambling (3), and aggression (4; 5). Harmful alcohol use is related to an increased risk of premature death and injuries, especially in young people (WHO, 2010).

Experimental studies demonstrate that alcohol impairs inhibitory motor control in stop-signal (SST) (6-9), and Go/Nogo tasks (10-12) that measure the ability to inhibit prepotent motor responses. Recently, alcohol consumption has been directly linked to alcohol-related impairment of inhibitory control in a Go/Nogo task: People with lower inhibitory control under alcohol consumed more alcohol in a free-access ASA experiment (13). Additionally, inhibitory control of binge drinkers was decreased in a Go/Nogo task under alcohol but not under placebo compared to moderate drinkers (14). A self-enhancing feedback loop between alcohol-induced impairment of inhibitory control and alcohol consumption has been suggested as a possible mechanism underlying loss of control during excessive drinking with negative long-term effects in susceptible people (cf, 12; 13).

Previous fMRI studies showed that alcohol decreased conflict-, and error-related activation of the anterior cingulate cortex (ACC) in a Go/Nogo (15) and Stroop task (16). During a SST, people at risk for alcoholism showed differential neural responses to moderate alcohol levels (BrAC ∼60 mg/dl). People with a low level of response to alcohol showed lower neural activation under alcohol in the left precentral gyrus, and higher activation in the left ACC (17), whereas people with a positive family history of alcoholism (FHA) showed no attenuation of brain responses under alcohol in anterior inferior frontal gyrus (IFG) compared to controls (18). However, both studies did not report overall alcohol effects on the neural response in inhibition-related brain areas. Thus, the neural mechanisms underlying the well-described alcohol-induced impairment of inhibitory control in healthy people (6-9) are still unknown.

Inhibitory control measured with a SST activates a right-dominant fronto-subcortical network including the right (R)IFG, bilateral anterior insulae, the pre-supplementary motor area (pre-SMA), the ACC, thalamic and striatal brain areas (19-23). This network was not only active during successful inhibitions as proposed earlier (24), but also during failed inhibitions indicating that response inhibition is triggered irrespective of the outcome of

inhibition trials during a tracking SST (22; 25), in which the probability of inhibition converges to 50% across the experiment. Further, the inhibition-related network has been delineated into functionally distinct parts: (i) a right ventral fronto-parietal portion including the RIFG/insula assumed to support the attentional capture of infrequent stop-signals (26; 27) and subsequent updating of action plans from response execution to inhibition (23; 28), (ii) the pre-SMA associated with the outright motor inhibition process via connections to the subthalamic/caudate nuclei (26; 27), and (iii) a bilateral frontal error-monitoring network including the ACC (24; 26) and anterior insulae during failed inhibition (29). A number of studies highlighted that decreased activation of the RIFG was linked to impaired inhibitory control (comparison of bad vs. good inhibitors, adolescents vs. adults, ADHD patients vs. controls, 19; 21; 29-31). Correspondingly, improved inhibitory control was associated with increased activation of the RIFG induced by pharmacological interventions (32), and transcranial current stimulation of the RIFG (33). Precise functional localization within the RIFG/insula in inhibitory control is still debated (19; 22; 23; 26; 28).

The present fMRI study is part of the “Dresden Longitudinal study on Alcohol use in Young Adults” (D-LAYA), which investigates the relation between laboratory free-access ASA and the early phase of drinking trajectories in young adults. This is one of the few studies investigating acute alcohol effects in healthy emerging adults at the beginning of their drinking “careers”. At this age, alcohol use is very common (34; 35), and high alcohol consumption might be indicative of future alcohol problems (36). However, the exact mechanisms why explorative drinking proceeds into risky and abusive forms in some people, and not in others (37), remains an unsolved question. Here, we investigated the effects of alcohol on inhibition-related brain responses using a tracking SST (25; 38) during fMRI. Alcohol was administered in a placebo-controlled cross-over design with alcohol levels clamped at 0.6 g/kg. We tested the hypothesis that alcohol decreases brain responses in the right frontal portion of the inhibition-related fronto-subcortical network that has been shown to be sensitive to impaired inhibitory control (21; 29-31), and thereby leads to alcohol-induced impairment of inhibitory control. Additionally, we measured cerebral perfusion using arterial spin labeling (ASL) MRI (39) to test whether alcohol effects on task-related blood oxygenation level-dependent (BOLD) responses were confounded by vasoactive alcohol effects on perfusion (40-42). Furthermore, we tested in the same sample whether alcohol-induced impairment of inhibitory control predicted alcohol consumption levels in a separate free-access ASA experiment (cf, 43).

Methods

Participants

Fifty healthy social drinkers performed the SST twice during fMRI within the framework of the D-LAYA study. Of those, 47 also took part in the free-access ASA experiment of the D-LAYA study that preceded the fMRI experiment (see supplement, “Recruitment”/“Sample characteristics”). For safety reasons, participants were only considered for fMRI if they had no MR-contraindications and if their maximum BrAC during one of the free-access sessions exceeded 0.5 g/kg. Further inclusion criteria were physical and mental health, habitual social drinking (>=2 drinks/week, at least one lifetime occasion of getting drunk), drug/alcohol

abstinence (at least one week/24h prior to each experimental day), positive or negative FHA (FHP: at least one first-degree biological relative affected by alcoholism; FHN: no first- or second-degree relative affected by alcoholism; see supplement, “Recruitment”). However, FHA was not the focus of the fMRI part. Exclusion criteria were a history of alcohol/“illicit drug” abuse/dependence, and pregnancy or breast-feeding in females.

For fMRI analysis, we excluded 8 data sets (reasons: head movement/sleepiness) resulting in a final sample of 42 right-handed participants (11 females, 15 FHP, mean age=19.1 years ±0.7, SD). Of those, 38 participants had valid free-access data for correlation with behavioral SST data from fMRI alcohol clamping (10 females, 15 FHP, mean age=18.9 years ±0.4, SD). All participants provided written consent and were paid 10€/hour. All study procedures were approved by the Ethics Committee of the Technische Universität Dresden.

Experimental procedures

On arrival, all participants had a BrAC of 0.0 g/kg (Dräger® Alcotest 6810 breathalyzer, Lübeck, Germany), and were tested negative for “illicit drug use” (see supplement “Sample characteristics”), and females for pregnancy.

Alcohol administration

In both experiments (free-access ASA/fMRI alcohol clamping), alcohol was administered intravenously using a 6% alcohol solution (v/v; mixture of normal saline with 95% ethanol [Braun, Melsungen, Germany]). Infusion rates were controlled using computer-assisted alcohol infusion systems (CAIS, 44).

For fMRI alcohol clamping, alcohol was administered in a single-blind, placebo-controlled cross-over design (placebo first: n=25; alcohol first: n=17; see Figure 1A). CAIS was used to reach a BrAC of 0.6 g/kg within 15 minutes after starting the infusion, and to maintain that level for the rest of the experiment by adjusting infusion rates based on BrAC measurements (Figure 1B; cf, 44). The placebo infusion consisted of normal saline.

Alcohol consumption was measured using an established free-access ASA paradigm (cf, 43; 45). Participants were instructed to produce pleasant alcohol effects like they would at a party with alcohol available for free, but to avoid unpleasant alcohol effects. Alcohol was requested by pressing a button which increased participants' arterial blood alcohol concentration by 7.5 mg%. A safety limit was set to 120 mg%.

BrAC was sampled regularly during the experiments. We developed a new method to obtain precise BrAC readings while participants lay in the MR-scanner (see supplement “Measurement of BrAC”).

Sequence of experiments (Figure 1A)

First, participants took part in two free-access ASA experiments that lasted approximately 145 minutes on separate days. Second, participants underwent fMRI alcohol clamping on two additional days. Imaging data were acquired with a 3T MR-scanner (Magnetom TrioTim; Siemens, Germany) equipped with a 12-channel head-coil (see supplement for

"MRI data acquisition"). On both days, MR-scanning started with measurement of absolute perfusion using ASL MRI at baseline before the infusion was started, continuously for 15 minutes while BrAC-levels increased, and before the SST (Figure 1B for fMRI timing). After reaching the target BrAC, the SST was performed (see "Stop-signal task").

On all days, alcohol administration started at the same time of day to control for circadian alcohol effects. Participants were sent home by taxi after BrAC dropped below 0.45 g/kg.

Stop-signal task

Figure 2 illustrates the SST. Participants responded to the direction of white arrows pointing left or right (go-signal; stimulus design adapted from Rubia *et al.* (24)) by pressing a button with their left or right index finger. Infrequently (20%), a white arrow pointing upwards (stop-signal) followed the presentation of the go stimulus with a time delay (stop-signal delay [SSD]). In this case, participants had to withhold the already triggered motor response. After every stop trial, the length of the SSD was adapted dynamically (+/- 50 ms) according to the participants' performance in the preceding stop trial (successful/failed inhibition; Figure 2) using a previously described tracking algorithm (25; 38). Using this tracking algorithm, the probability of inhibition (PI: #stop success/#all stop trials) converged to 50% after 10-15 stop trials, and fluctuated around 50% for the remaining trials. We estimated the SSRT, the latency of response inhibition, by rank ordering Go RTs and subtracting the mean SSD (reflecting the start of motor inhibition) from the n^{th} Go RT corresponding to the percentile of the probability of response in stop trials (reflecting the finishing time of motor inhibition; cf, 18; 29; 46; for a review, 47). This SSRT estimation method accounts for deviations of "PI" from 50% that may occur among participants.

Trials were separated by short jittered inter-trial intervals (mean=900 ms, range: 700-1100 ms; adopted from Whelan et al. (29)). Stop trials appeared every 2 to 7 go trials (on average every 8.6 seconds; range=3.7–13.4s) allowing for hemodynamic separation of stop trials. Direction of go stimuli (left/right) was equally distributed in go and stop trials. For timing/task specifications, see Figure 2. We used Presentation® (Neurobehavioral Systems, Albany, USA) for task presentation and recording of motor responses.

Data analysis

Behavioral data were analyzed with SPSS21 (IBM, NY, USA), and fMRI data with statistical parametric mapping (SPM8, Wellcome Trust Centre for Neuroimaging, London, UK). In the following, "alcohol effect" depicts the difference of "alcohol-placebo".

fMRI alcohol clamping

Behavioral data—Our main emphasis was placed on alcohol effects on inhibitory control reflected by the SSRT. Additional SST-variables were mean Go RT, PI, and go trial accuracy. We compared alcohol to placebo responses with paired t-tests, and computed alcohol-induced impairment of inhibitory control ($SSRT_{alcohol}$–$SSRT_{placebo}$) for additional analyses.

Imaging data (for "Preprocessing", see supplement)—On the first level, we modeled successful (StopInhibit), and failed (StopFail) stop trials, as well as go error trials (4%/go trials) as separate events for placebo and alcohol using a general linear model (GLM) with realignment parameters included as nuisance variables (3 translation, 3 rotation parameters). Correct go trials were represented within the implicit baseline of the GLM (cf, 24; 29-31). They were not modeled explicitly because they appeared with high-frequency during the rapid event-related fMRI experiment (1.7-2.1 seconds). In 1% (SD=3%) of stop trials, a response was given before the stop-signal would have appeared. In these trials, the presentation of the stop-signal was omitted and the SSD for the next stop trial was decreased by 50 ms. Since participants perceived these trials as "normal" go trials, we modeled brain responses accordingly. For each regressor, the onsets of the go-signals were convolved with SPM8's canonical hemodynamic response function. We corrected for serial auto-correlations using an AR(1)-model.

On the second level, we subjected the first-level contrasts "StopInhibit" and "StopFail" above the implicit go baseline (i.e., contrasted against correct go trials) for placebo and alcohol to a 2×2 full-factorial model with the within-subject factors stopping (StopInhibit, StopFail) and drug (alcohol, placebo). According to Boehler *et al.* (22), we first computed a whole-brain conjunction analysis of "StopInhibit" and "StopFail" across both drug conditions to confirm that the fronto-subcortical motor inhibition network (i.e., bilateral IFG, insulae, thalamus, pre-SMA, basal ganglia) was active in stop trials irrespective of the outcome. We refer to findings from this conjunction analysis as "inhibition-related" brain areas/responses. Additionally, we compared activity between "StopInhibit" and "StopFail". We expected activation differences in brain areas associated with error- and conflict-monitoring (bilateral insulae, ACC) for "StopFail>StopInhibit", and less prominent differences for "StopInhibit>StopFail" as both stop conditions trigger motor inhibition (22).

Second, to identify inhibition-related brain areas affected by alcohol, we performed a whole-brain conjunction analysis of the contrasts "alcohol<placebo", "StopInhibit", and "StopFail". Then, we extracted brain responses in the resulting areas (two regions: RIFG/Insula, volume=4048.3 mm^3, occipito-temporal cortex, volume=2790.6 mm^3) for first-level contrasts ("StopInhibit" and "StopFail" for alcohol and placebo) to test whether alcohol effects within these regions ($[StopInhibit+StopFail]_{alcohol} - [StopInhibit+StopFail]_{placebo}$) were correlated with alcohol-induced impaired inhibitory control.

For each participant, we computed global and local (i.e., inhibition-related areas affected by alcohol) perfusion measured before the SST (see supplement for "ASL data-analysis"), and assessed alcohol effects on perfusion using paired t-tests. To check whether alcohol effects on inhibition-related BOLD responses were confounded by alcohol effects on perfusion (global/local), we calculated path analyses (Figure S2, supplement) using AMOS 21 (IBM).

Alcohol-induced impairment of inhibitory control and free-access alcohol consumption

We correlated alcohol-induced impairment of inhibitory control with number of alcohol requests (NoAR) during free-access ASA. We focused on NoAR of the second free-access session because the first session may be biased by unspecific exploratory behavior (see, 43; 45). This was supported by the fact that drinks per drinking day assessed by a time-line

follow-back interview (48) significantly correlated with NoAR from the second day (Spearman's $r(36)=.44$, $p=.006$), but not the first (Spearman's $r(36)=.25$, $p=.13$). We used NoAR as a measure of free-access alcohol consumption for association with alcohol-induced impaired inhibitory control because it also involved a motor response. NoAR was also highly correlated with free-access BrAC-levels ($r>.90$).

Before statistical analysis, we verified that potentially confounding variables such as FHA, gender, drug order, current smoking, and "illicit drug use" did not significantly influence alcohol effects on inhibitory control and inhibition-related brain responses, and free-access alcohol consumption (see supplement "Results, Between-subject variables"). Thus, we did not include those covariates into statistical analyses. Imaging data were thresholded at $p<.001$ (uncorrected) with at least 50 connected voxels.

Results

fMRI alcohol clamping

Alcohol effects on behavior—Alcohol significantly increased the SSRT by 18.4 ms, while the mean Go RT was not affected by alcohol (Table 1). Acute alcohol intoxication decreased the PI (-1.9%), and the proportion of correct go trials (-1.4%, Table 1). BrAC pre and post SST are shown in Figure 1B.

Whole-brain analyses (2×2 full-factorial model)

Inhibition-related brain responses: The whole-brain conjunction of "StopInhibit" and "StopFail" (above the implicit go baseline) revealed robust inhibiton-related activation of a right dominant fronto-subcortical network and bilateral occipito-temporo-parietal cortex (Figure 3; Table 2A). *Comparison of stop conditions:* "StopInhibit" elicited increased activation in left middle, and inferior frontal cortex, in occipito-parietal cortex, and the cerebellum compared to "StopFail" (Figure 3, Table 2B). In contrast, "StopFail" increased brain responses in bilateral precentral gyrus and anterior insulae, medial frontal, temporal and motor-related brain areas compared to "StopInhibit" (Figure 3, Table 2C).

Alcohol effects on inhibition-related brain responses: The whole-brain conjunction analysis of "alcohol<placebo", "StopInhibit", and "StopFail" revealed that alcohol decreased inhibition-related brain responses in two clusters: the RIFG/anterior insula, and the right middle occipito-temporal cortex (Figure 4ABC, Table 2D). Further, no brain area showed increased inhibitory activation under alcohol (versus placebo), and no interaction between stopping and drug emerged indicating that alcohol effects did not differ between stopping conditions (see supplement, Table S2).

Association of alcohol effects on regional inhibition-related brain responses and inhibitory control

For regional analyses, we extracted mean brain responses in the RIFG/Insula and occipito-temporal cortex (see Figure 4BC), and collapsed alcohol effects across stopping conditions ($[\text{StopInhibit+StopFail}]_{\text{alcohol}} - [\text{StopInhibit+StopFail}]_{\text{placebo}}$). Alcohol effects on inhibition-related brain responses in the RIFG/insula (Figure 4D; Pearson's $r(40)=-.35$, $p=.024$), and

the occipito-temporal cortex (Figure 4E; Pearson's $r(40)=-.33$, $p=.032$) correlated negatively with alcohol-induced impaired inhibitory control. The negative correlation indicates larger activation decreases with worsened inhibitory control under alcohol. The correlation within the occipito-temporal cortex did not survive correction of the α-level for multiple testing (number of tests=2).

Furthermore, global and local (RIFG/insula, occipito-temporal cortex) cerebral perfusion measured before the SST increased significantly under alcohol (supplement, Table S3). Path analyses for the RIFG/insula, and occipito-temporal cortex showed that perfusion alcohol effects neither significantly influenced alcohol effects on inhibition-related BOLD responses, nor on inhibitory control (supplement Table S4, Figure S2). As indicated by brain-behavior correlations, only alcohol effects on inhibition-related BOLD responses in the RIFG/Insula and the occipito-temporal cortex significantly mediated alcohol-induced impairment of inhibitory control (Table S4).

Alcohol-induced impairment of inhibitory control and free-access alcohol consumption

Alcohol-induced impairment of inhibitory control during fMRI alcohol clamping correlated positively with NoAR of free-access ASA (Spearman's $r(36)=.37$, $p=.02$; Figure 5). Thus, larger impairment of inhibitory control under alcohol was linked to more alcohol requests in the free-access experiment.

Discussion

In the present study, moderate alcohol intoxication impaired inhibitory control indicated by longer SSRTs, and decreased inhibition-related brain responses in inhibition-related right fronto-temporal areas. Importantly, participants with pronounced impaired inhibitory control under alcohol showed a greater blunting of inhibition-related brain responses in the RIFG/insula and the right occipito-temporal cortex, and consumed more alcohol during free-access ASA.

Alcohol decreased inhibition-related brain responses in the RIFG/insula and the occipitotemporal cortex, two areas belonging to the right ventral fronto-parietal attention network (49; 50). The cluster encompassing the RIFG and anterior insula matches the brain area that was active during inhibitory control across SST *and* Go/Nogo tasks (19; 23). Recent evidence suggests that during inhibitory control the RIFG/insula might subserve cognitive processes that precede actual motor inhibition: the attentional capture of infrequent stop-signals (26; 27; 49; 50), and subsequent updating of action plans from response execution to inhibition (especially linked to the pars opercularis 23; 28). The anterior insula has not only been linked to detecting salient events (23; 51), and maintenance of task set (52), but also to error-monitoring (compare Figure 3; 53-55). We assume that during inhibitory control the RIFG and anterior insula are co-activated (cf. also, 26) and mediate attention and updating processes. However, precise functional localization within the RIFG/Insula in inhibitory control is still debated (19; 22; 23; 26; 28). Activation of the occipito-temporal cortex during inhibitory control likely reflects visual attention processes triggered by the visual modality of stop-signals (cf, 22).

Larger decreases of inhibition-related brain responses in the RIFG/insula and the occipitotemporal cortex under alcohol were linked to more pronounced alcohol-induced impairment of inhibitory control. Previous studies related decreased activation of the RIFG with low inhibitory control in general (21; 29-31), and in anterior RIFG across placebo *and* alcohol conditions (18). While alcohol decreased inhibition-related activation in the anterior portion of the RIFG in FHN people only, a higher risk for alcoholism in FHP participants was linked to less neural reactivity to alcohol (18). Compared to this population-specific alcohol effect in anterior RIFG, we observed a robust main effect of alcohol in the RIFG/Insula, a crucial area for inhibitory control (19; 23). Specifically, alcohol-induced impairment of inhibitory control, depicting the difference of "alcohol-placebo", was linked to decreased inhibition-related brain responses in the RIFG/insula under alcohol compared to placebo. Noteworthy, FHA neither affected behavioral, nor neural alcohol effects in our study, which could be explained by a younger sample and the fact that we did not match our participants on FHA.

In the current study, alcohol effects on inhibition-related brain responses did not differ between stopping conditions. This gives rise to the assumption that during inhibitory control alcohol acts on the attentional capture of stop-signals and subsequent initiation of motor inhibition (23; 26-28), processes present in both conditions that precede motor inhibition. We do not assume that alcohol impaired the attention capacity in general, since the mean Go RT was not affected by alcohol (cf, 6). Our results underline that during inhibitory control alcohol affects cognitive control processes indicated by decreased brain responses in prefrontal areas (compare also, 15; 16; 18), and not directly motor inhibition associated with subcortical areas and the pre-SMA (26; 27).

Furthermore, impaired inhibitory control under alcohol predicted free-access alcohol consumption with people who were more impaired under alcohol, consuming also more alcohol. Importantly, low inhibitory control under alcohol was the only significant predictor of free-access alcohol consumption in a "post-hoc backward regression analysis" (see supplement) with the predictors "$SSRT_{placebo}$", subjective perceptions of alcohol, and saccadic latency (variables significantly affected by alcohol (e.g., 56-58); supplement, "Level of alcohol intoxication": Tables S5/S6). This finding corroborates that low inhibitory control under alcohol might be a specific mechanism underlying dysfunctional drinking (12-14). One might assume that the neural correlates of impaired inhibitory control under alcohol would also predict free-access alcohol consumption. This was however not the case and could possibly be explained by the fact that alcohol affected fronto-temporal, and not stopping-related pre-motor and subcortical areas. To further explore if alcohol also affects stopping-related areas and if this would specifically interact with free-access alcohol consumption, future studies might use SST versions delineating attention and updating processes from motor inhibition itself (26; 28). Possibly, higher alcohol doses would affect the subcortical motor inhibition system. Furthermore, participants showed high alcohol consumption in the laboratory (maximum BrAC∼0.9 g/kg), and in real life (Table S1, supplement) although not meeting the criteria for alcohol use disorders. This might have reduced the bandwidth of alcohol consumption levels required to establish a correlation between two independently acquired measures.

It is a limitation of this and other pharmacological BOLD-fMRI studies that group differences in baseline perfusion or metabolic activity may cause alterations of BOLD responses that are not due to task-related neural activity (42; 59; 60). In our data, we observed lower average task-related BOLD responses with higher baseline perfusion. Such effects could be responsible for the observed alcohol effects on regional BOLD responses in the RIFG/insula and occipito-temporal cortex, and on inhibitory control. However, path analyses showed that only alcohol effects on regional BOLD responses were significantly linked to alcohol-induced impairment of inhibitory control (Figure S2/Table S4). Increased perfusion under alcohol neither significantly influenced alcohol effects on regional BOLD responses (RIFG/Insula, occipito-temporal cortex), nor on inhibitory control. We conclude that alcohol effects on regional BOLD responses are likely due to changes in task-related neural activity, though we cannot completely disentangle vascular effects from task-related changes of neural activity with our methodology. To explore this, one might use quantitative or calibrated BOLD imaging (59; 61), which would allow to estimate changes in the metabolic rate of oxygen. For reasons of experimental complexity, we did not measure heart rate, respiration, and blood pressure that might also have contributed to disentangle cardiovascular from neural alcohol effects.

Conclusion

Alcohol affects the attentional capture of stop-signals and subsequent updating of action plans from response execution to inhibition, cognitive processes that precede motor inhibition, indicated by decreased brain responses in the RIFG/insula and occipito-temporal cortex. Still, precise functional localization within the RIFG/insula is debated. Under alcohol, diminished attentional capture of stop-signals might slow down initiation of motor inhibition which might impair inhibitory control via functional connections between the RIFG/insula and the pre-SMA (26; 27). In turn, alcohol-induced impairment of inhibitory control may enhance free-access alcohol consumption. We suggest that these processes interact and form a self-enhancing loop in which more alcohol consumption leads to lower inhibitory control and vice versa. Young adults with low inhibitory control under alcohol might consume more alcohol which might promote alcohol-related problems in the future (36; 37).

At the age of 21, we will test in the same participants whether alcohol-related impairment of inhibitory control and attenuated inhibition-related brain responses can predict free-access alcohol consumption that may have escalated in some and went back to normal in others. Further, we will study whether behavioral and neural correlates of alcohol-related impairment of inhibitory control are linked to other dysfunctional behaviors such as alcohol-induced aggression, or risk taking.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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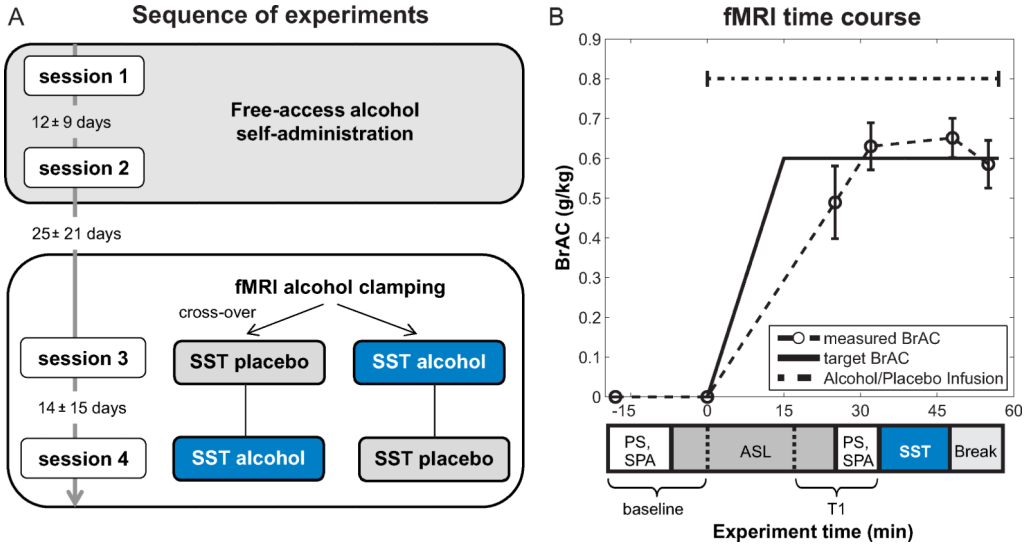

Figure 1.

Sequence of experiments and fMRI time course. A: The experiment consisted of four sessions. First, we conducted free-access alcohol self-administration on two separate days (session 1+2). Second, the SST was performed during fMRI alcohol clamping, once under a constant alcohol exposure of 0.6 g/kg, and once under placebo (session 3+4). The order of the alcohol and placebo condition in the fMRI alcohol clamping part was randomized across participants. B: Timing of the fMRI alcohol clamping experiment with target and measured BrACs (mean, Error bars represent standard deviations). We also measured subjective perceptions of alcohol (SPA) and saccadic eye-movements (PS) at baseline and before the SST at T1 to track the "Level of alcohol intoxication" (see supplement). After the break, the experiment continued with other tasks (see supplement Figure S1 for complete time course). *Abbreviations:* ASL = arterial spin labeling, BrAC = breath alcohol concentration, PS = prosaccades, SPA = subjective perception of alcohol, SST = stop-signal task, T1 = time 1.

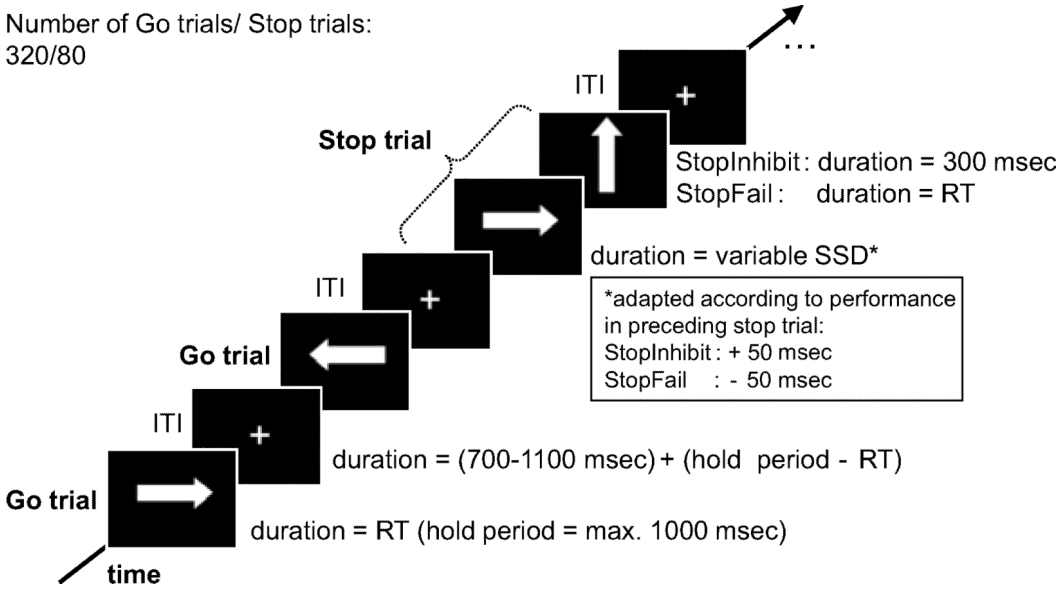

Figure 2.

Timing of the SST. In go trials, the go stimulus was displayed until a response was recorded, but for a maximum of 1000 ms. In stop trials, the go stimulus was presented for the duration of the variable stop-signal delay (SSD; mean ±SD: alcohol = 184 ms ± 91; placebo = 196 ms ±85) followed by the stop-signal for 300 ms in successful stop trials (StopInhibit) or until a response was recorded in failed stop trials (StopFail). Go and stop trials were followed by the presentation of a central fixation cross for the duration of a jittered inter-trial interval (ITI, mean=900ms). In stop trials, the SSD (initial SSD=200 ms) was adapted dynamically according to the performance in the preceding stop trial (cf, 36): If participants successfully inhibited the response, the SSD was increased by 50 ms, if they failed to inhibit the response, the SSD was decreased by 50 ms. The SST lasted for 13 minutes. ms = milliseconds, occ/temp = occipito-temporal cortex, RT = reaction time, SD = standard deviation.

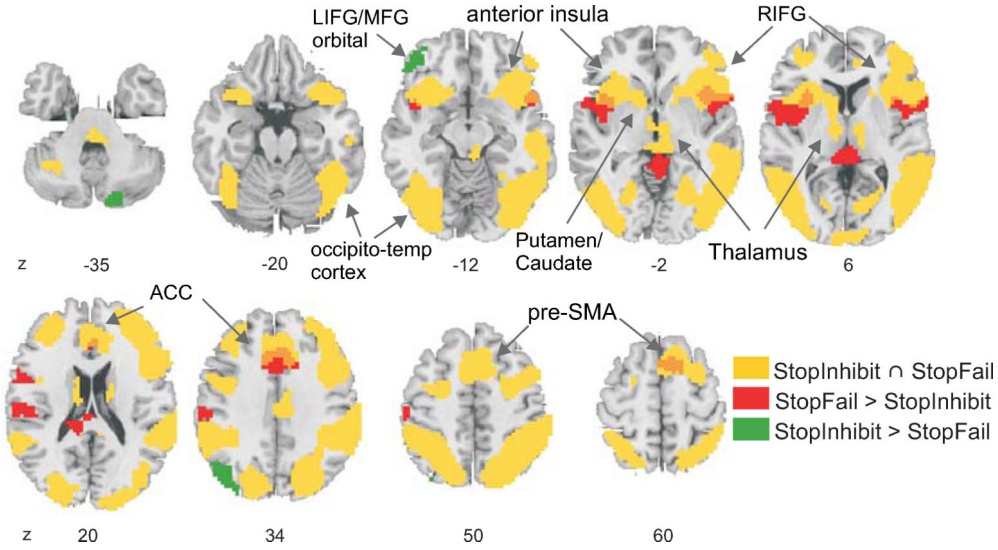

Figure 3.

Activation of the fronto-subcortical motor inhibition network and bilateral occipito-temporo-parietal cortex during stop trials. Brain areas that were active across both stopping conditions (conjunction of StopInhibit and StopFail) are shown in yellow. Increased brain activation for StopInhibit is shown in green (StopInhibit > StopFail) and for StopFail in red (StopFail > StopInhibit). Some brain areas showed overlapping activation for both stopping conditions and increased activation for StopFail > StopInhibit, this is shown in orange. Voxel-wise significance threshold: $p<.001$ uncorrected with at least 50 connected voxels.

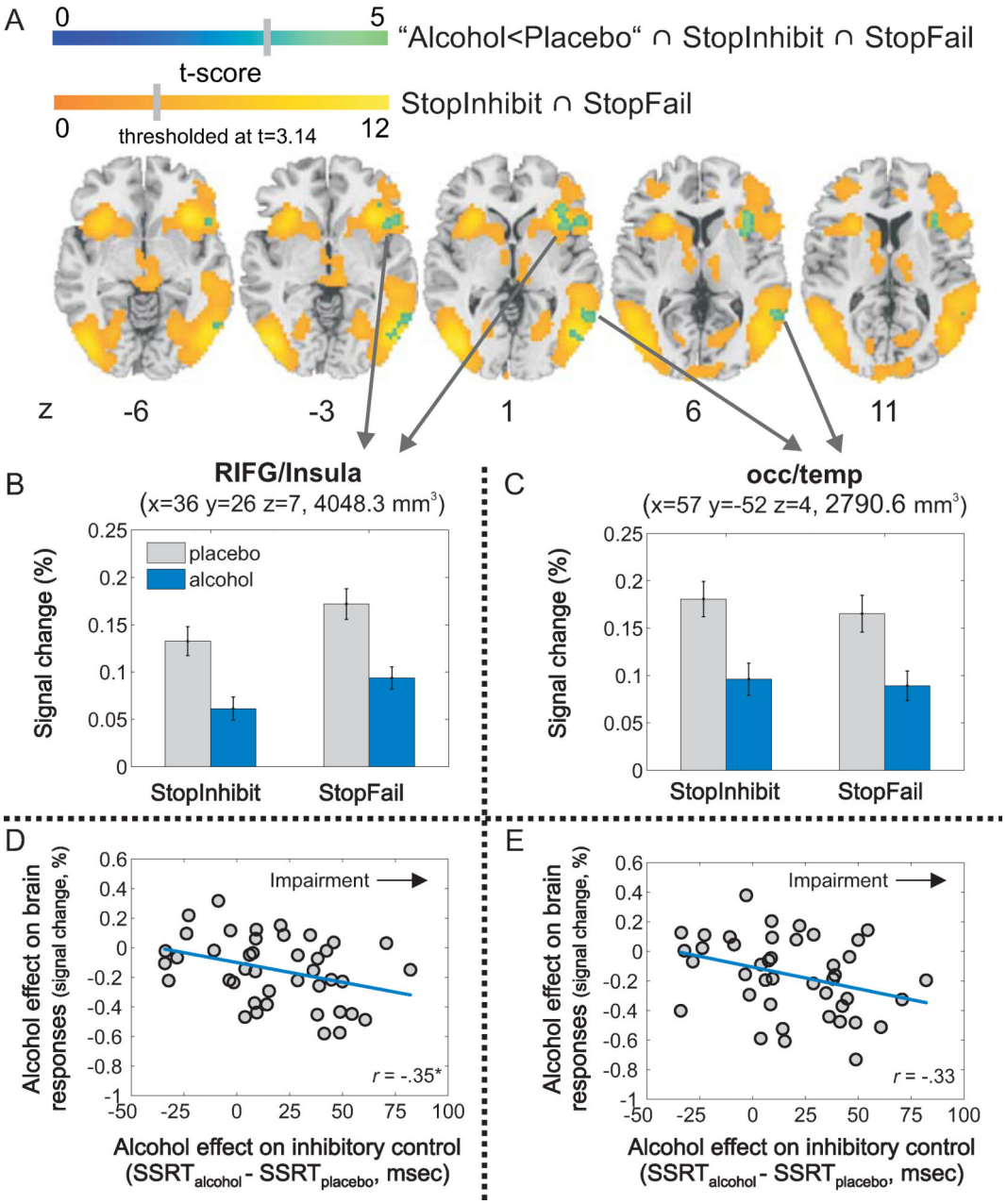

Figure 4. Whole-brain conjunction analysis

(A) Alcohol effects (alcohol<placebo) on inhibition-related brain responses (StopInhibit ∩ StopFail). Brain maps showing the alcohol effect (blue color scale) overlaid on inhibition-related brain responses (yellow-orange color scale; significance threshold: $p<.001$ uncorrected, k>50). Mean brain responses for StopInhibit and StopFail (above the implicit go baseline) for alcohol and placebo are displayed for the two inhibition-related brain areas that exhibited decreased activation under alcohol in the whole-brain conjunction analysis: RIFG/insula (B), and the occipito-temporal cortex (C). *Regional analyses*: Correlation between alcohol-induced impairment of inhibitory control (SSRTalcohol-SSRTplacebo; >0: impaired; <0: improved) and alcohol effects on regional inhibition-related brain responses in

the RIFG/insula (D), and the occipitotemporal cortex (E). Error bars represent the standard error of the mean. Locations are given in MNI-space. *Abbreviations:* mm^3 = cubic millimeter, ms = milliseconds, occ/temp = occipito-temporal cortex, *r* = Pearson correlation coefficient, RIFG = right inferior frontal gyrus, SSRT = stop-signal reaction time, * = $p <$ .025 (α-level corrected for multiple testing, p=.05/[number of tests=2]).

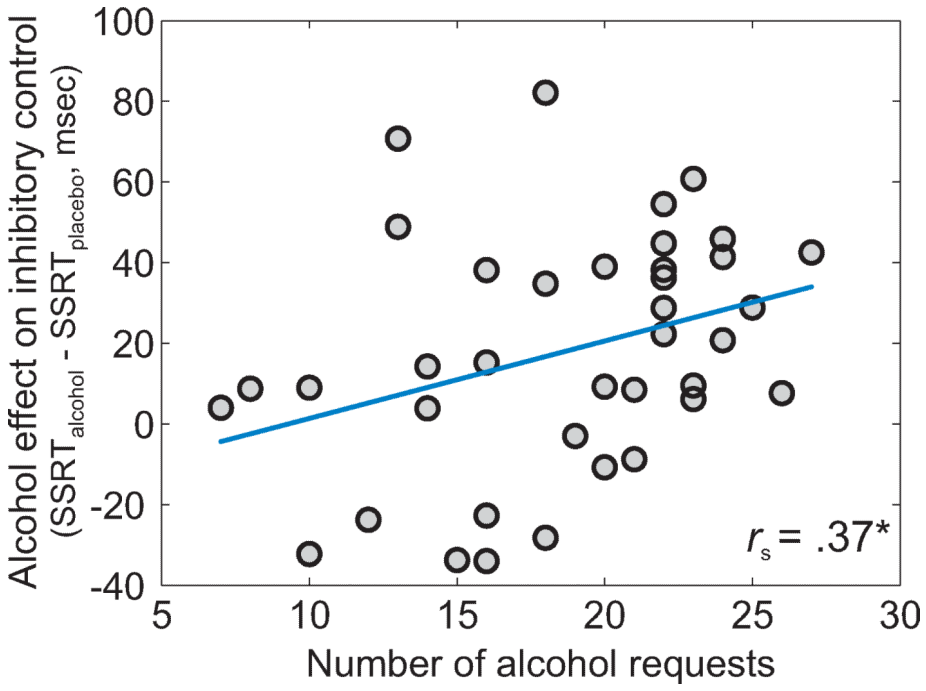

Figure 5.

Correlation between alcohol-induced impairment of inhibitory control at 0.6 g/kg during fMRI alcohol clamping and number of alcohol requests during free-access ASA (n=38, valid free-access data). *Abbreviations:* ms = milliseconds, r_s = Spearman correlation coefficient, SSRT = stop-signal reaction time, * = p <.05.

Table 1

Effects of alcohol on behavioral SST outcome variables during fMRI alcohol clamping. Alcohol and placebo responses were compared with paired t-tests (*t*).

	Placebo		**Alcohol**		**test-statistics**
	Mean	***(SEM)***	***Mean***	***(SEM)***	**placebo vs. Alcohol**
SSRT (ms)***	207.6	(6.3)	226.0	(8.1)	$t(41) = -4.07$, $p<.001$
Probability of inhibition (%)**	48.2	(0.5)	46.2	(0.8)	$t(41) = 2.97$, $p=.005$
mean Go RT (ms)*n.s.*	414.9	(9.6)	419.1	(10.0)	$t(41) = -.88$, $p=.383$
Correct Go trials (%)**	96.9	(0.4)	95.5	(0.5)	$t(41) = 3.35$, $p=.002$

Abbreviations:

*** = $p<.001$,

** = $p<.01$,

n.s. = not significant,

SEM = standard error of the mean

Table 2

Results from the 2 (stopping: StopInhibit, StopFail)×2 (drug: alcohol, placebo) full-factorial model. Brain areas that showed (A) overlapping activation in both stop conditions, (B+C) differential activation between StopInhibit, and StopFail, and (D) decreased inhibition-related brain responses under alcohol compared to placebo. P-values corrected for multiple comparisons (FWE at cluster and peak level), T-values and MNI coordinates are shown. Whole-brain significance threshold: p <.001 (uncorrected) with at least 50 connected voxels.

			MNI coordinates			cluster level		peak level	
Brain area		**BA**	**x**	**y**	**z**	**FWE-corr.**	**k**	**FWE-corr.**	**T**
(A) Inhibition-related brain responses (Conjunction of StopInhibit and StopFail above the implicit go baseline)									
L	MOG	19	-45	-76	1	<0.001	3253	<0.001	11.46
L	Fusiform G	37	-42	-58	-14				8.89
L	MTG	39	-54	-58	7				8.76
R	ITG	37	51	-67	-2	<0.001	4804	<0.001	11.39
R	IPL	40	33	-49	46				9.42
R	MOG	19	30	-73	28				9.38
R	IFG/Insula	47	33	23	-5	<0.001	4088	<0.001	11.29
R	IFG	9	48	11	28				7.69
R	Cingulate G	32	9	29	31				7.48
L	Insula	-	-30	20	4	<0.001	1138	<0.001	8.91
L	IFG/Insula	47	-36	17	-8				8.91
R	Thalamus	-	6	-28	-5				6.12
L	MFG	46	-39	35	28	<0.001	457	<0.001	6.15
L	MFG	10	-33	50	19				5.90
L	MFG	6	-24	-4	49	<0.001	422	<0.001	5.63
L	IFG	9	-42	5	25				5.47
L	IFG	9	-48	2	34				5.19
R	Cingulate G	23	3	-22	28	0.001	168	<0.001	5.59
L	Post. Cingulate	23	-3	-31	25				4.57
R	Post. Cingulate	23	6	-40	22				3.74
(B) StopInhibit > StopFail									
R	Cerebellum/Uvula	-	15	-85	-35	0.141	51	0.035	4.86
L	MFG	11	-45	44	-11	0.062	69	0.166	4.41

Brain area		BA	MNI coordinates x	y	z	cluster level FWE-corr.	k	peak level FWE-corr.	T
L	IFG	47	-51	38	-14			0.362	4.14
L	IFG	47	-36	32	-17			0.949	3.51
L	MOG	19	-36	-82	40	0.008	118	0.341	4.17
L	Angular G	39	-45	-76	28			0.669	3.86
L	SOG	19	-36	-85	31			0.906	3.59
(C) StopFail > StopInhibit									
L	Precentral G	6	-57	5	13	<0.001	417	0.001	5.68
L	Insula	-	-36	8	4			0.034	4.86
L	STG	22	-57	-7	7			0.976	3.42
L	Postcentral G	43	-63	-19	22	0.001	191	0.003	5.44
L	Precentral G	4	-60	-22	43			0.078	4.64
R	Insula	13	45	11	-2	<0.001	251	0.007	5.26
R	Precentral G	44	48	2	10			0.121	4.51
R	STG	22	60	8	4			0.213	4.33
L	Cingulate G	32	-6	20	34	<0.001	205	0.008	5.23
L	ACC	24	0	29	25			0.719	3.81
	Cerebellum	-	0	-31	10	<0.001	205	0.165	4.42
L	Culmen	-	0	-43	-2			0.353	4.15
L	Pulvinar	-	-12	-37	16			0.525	3.99
R	SMA	6	9	11	61	0.148	50	0.209	4.34
(D) Alcohol<placebo in inhibition-related brain areas (Conjunction of alcohol<placebo, StopInhibit, and StopFail)									
R	IFG	45	36	26	7	0.015	103	0.103	4.56
R	Insula	-	33	14	7			0.14	4.47
R	IFG	47	51	20	1			0.773	3.76
R	MTG	21	57	-52	4	0.056	71	0.372	4.13
R	MTG	21	66	-49	4			0.95	3.51
R	MOG	37	51	-70	1			0.994	3.3

Abbreviations: ACC = anterior cingulate cortex, BA=Brodmann area, G=gyrus, IFG = inferior frontal gyrus, IPL = inferior parietal lobe, ITG = inferior temporal gyrus, MOG = middle occipital gyrus, MTG = middle temporal gyrus, SOG = superior occiptal gyrus; SMA = supplementary motor area, STG = superior temporal gyrus