Alcohol-Induced Impairment of Inhibitory Control Is Linked to Attenuated Brain Responses in Right Fronto-Temporal Cortex

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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 50 young adults with a stop-signal task during functional magnetic resonance imaging. In a single-blind placebo-controlled cross-over design, all participants performed the stop-signal task once under alcohol with a breath alcohol concentration of .6 g/kg and once under placebo. In addition, alcohol consumption was assessed with a free-access alcohol self-administration paradigm in the same participants.

Results: Inhibitory control was robustly decreased under alcohol compared with placebo, indicated by longer stop-signal reaction times. 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.

Conclusions: 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 might enhance alcohol consumption in young adults, which might promote future alcohol problems.

Key Words: Acute alcohol intoxication, alcohol consumption, fMRI, inhibitory control, response inhibition, stop-signal task

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 (World Health Organization, 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 alcohol self-administration (ASA) experiment (13). Additionally, inhibitory control of binge drinkers was decreased in a Go/Nogo task under alcohol but not under placebo compared with 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 (12,13).

Previous functional magnetic resonance imaging (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 an SST, people at risk for alcoholism showed differential neural responses to moderate alcohol levels (breath alcohol concentration [BrAC] of approximately 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 compared with control subjects (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 an SST activates a right-dominant fronto-subcortical network, including the right inferior frontal gyrus (RIFG), bilateral anterior insulae, the pre-supplementary motor area (pre-SMA), the ACC, and thalamic and striatal brain areas (19–23). This network was active not only 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 (PI) converges to 50% across the experiment. Furthermore, the

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inhibition-related network has been delineated into functionally distinct parts: 1) 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); 2) the pre-SMA associated with the outright motor inhibition process via connections to the subthalamic/caudate nuclei (26,27); and 3) 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, attention-deficit/hyperactivity disorder patients vs. control subjects) (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 D-LAYA study (Dresden Longitudinal Study on Alcohol Use in Young Adults), 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 with a tracking SST (25,38) during fMRI. Alcohol was administered in a placebo-controlled cross-over design with alcohol levels clamped at .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 with arterial spin labeling (ASL) MRI (39) to test whether alcohol effects on task-related blood oxygen 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 (43).

Methods and Materials

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 (for Recruitment/Sample Characteristics see Supplement 1). For safety reasons, participants were only considered for fMRI if they had no magnetic resonance (MR)-contraindications and if their maximum BrAC during one of the free-access sessions exceeded .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 1 week/24 h before each experimental day), positive (at least one first-degree biological relative affected by alcoholism) or negative (no first- or second-degree relative affected by alcoholism) FHA (see Recruitment in Supplement 1). However, FHA was not the focus of the fMRI experiment. Exclusion criteria were a history of alcohol/illicit drug abuse/dependence and pregnancy or breast-feeding in women.

For fMRI analysis, we excluded 8 datasets (reasons: head movement/sleepiness) resulting in a final sample of 42 right-handed participants (11 women, 15 positive FHA, mean age = 19.1 years ± .7, SD). Of those, 38 participants had valid free-access data for correlation with behavioral SST data from fMRI alcohol clamping (10 women, 15 positive FHA, mean age = 18.9 years ± .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 g/kg (Dräger Alcotest 6810 breathalyzer; Lübeck, Germany) and were tested negative for illicit drug use (see Sample Characteristics in Supplement 1), and women were tested negative for pregnancy.

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

For fMRI alcohol clamping, alcohol was administered in a single-blind, placebo-controlled cross-over design (placebo first: $n = 25$; alcohol first: $n = 17$) (Figure 1A). Computer-assisted alcohol infusion systems were used to reach a BrAC of .6 g/kg within 15 min after starting the infusion and to maintain that level for the rest of the experiment by adjusting infusion rates on the basis of BrAC measurements (Figure 1B) (44). The placebo infusion consisted of normal saline.

Alcohol consumption was measured with an established free-access ASA paradigm (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 arterial blood alcohol concentration of participants by 7.5 mg%. A safety limit was set to 120 mg%.

The 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 Measurement of BrAC in Supplement 1).

Sequence of Experiments. First, participants took part in two free-access ASA experiments that lasted approximately 145 min on separate days (Figure 1A). Second, participants underwent fMRI alcohol clamping on two additional days (Figure 1A). Imaging data were acquired with a 3T MR-scanner (Magnetom TrioTim; Siemens, Erlangen, Germany) equipped with a 12-channel head-coil (see MRI Data Acquisition in Supplement 1). On both days, MR-scanning started with measurement of absolute perfusion. ASL MRI was measured at baseline before the infusion was started, continuously for 15 min while BrAC-levels increased, and before the SST (see Figure 1B for fMRI timing). After reaching the target BrAC, the SST was performed (see Stop-Signal Task, below).

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 .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