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

Gabriela Gan, Alvaro Guevara, Michael Marxen, Maike Neumann, Elisabeth Jünger, Andrea Kobiella, Eva Mennigen, Maximilian Pilhatsch, Daniel Schwarz, Ulrich S. Zimmermann, and Michael N. Smolka

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

From the Department of Psychiatry and Neuroimaging Center (GG, AG, MM, MN, EJ, AK, EM, MP, DS, USZ, MNS), Technische Universität Dresden, Dresden, Germany; and the Escuela de Matemática (AG), Universidad de Costa Rica, San José, Costa Rica.

Address correspondence to Michael N. Smolka, M.D., Department of Psychiatry and Neuroimaging Center, Technische Universität Dresden, Würzburger Str. 35, 01187 Dresden, Germany; E-mail: michael.smolka@tu-dresden.de.

Received Mar 8, 2013; revised Dec 19, 2013; accepted Dec 21, 2013.

0006-3223/$36.00
http://dx.doi.org/10.1016/j.biopsych.2013.12.017

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

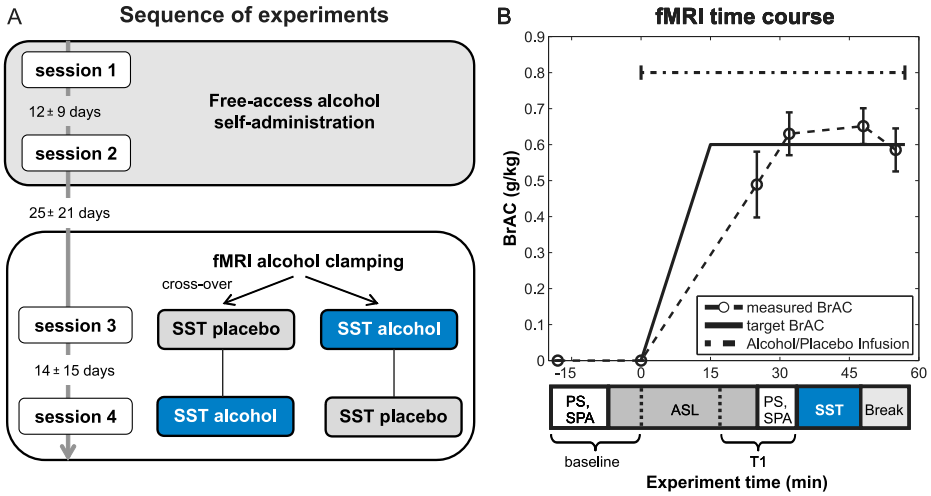

Figure 1. Sequence of experiments and functional magnetic resonance imaging (fMRI) time course. **(A)** The experiment consisted of four sessions. First, we conducted free-access alcohol self-administration on two separate days (session 1+2). Second, the stop-signal task (SST) was performed during fMRI alcohol clamping, once under a constant alcohol exposure of .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 breath alcohol concentration (BrAC) (mean, error bars represent SDs). We also measured subjective perceptions of alcohol (SPA) and saccadic eye-movements (PS) at baseline and before the SST at time 1 (T1) to track the Level of Alcohol Intoxication (Supplement 1). After the break, the experiment continued with other tasks (see Figure S1 in Supplement 1 for complete time course). ASL, arterial spin labeling.

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 msec) according to the performance of the participants in the preceding stop trial (successful/failed inhibition) (Figure 2) with a previously described tracking algorithm (25,38). With this tracking algorithm, the probability of inhibition (PI: n stop success/n all stop trials) converged to 50% after 10–15 stop trials and fluctuated around 50% for the remaining trials. We estimated the stop-signal reaction time (SSRT), the latency of response inhibition, by rank ordering Go reaction times (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) (18,29,46) (for a review, 47). This SSRT estimation method accounts for deviations of PI from 50% that might occur among participants.

Trials were separated by short jittered inter-trial intervals (mean = 900 msec, range: 700–1100 msec) [adopted from Whelan *et al.* (29)]. Stop trials appeared every 2–7 go trials (on average every 8.6 sec; range = 3.7–13.4 sec) 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, California) for task presentation and recording of motor responses.

Data Analysis

Behavioral data were analyzed with SPSS21 (IBM, Armonk, New York), and fMRI data were analyzed with statistical parametric mapping (SPM8; Wellcome Trust Centre for Neuroimaging, London, United Kingdom). In the following, "alcohol effect" depicts the difference of "alcohol-placebo."

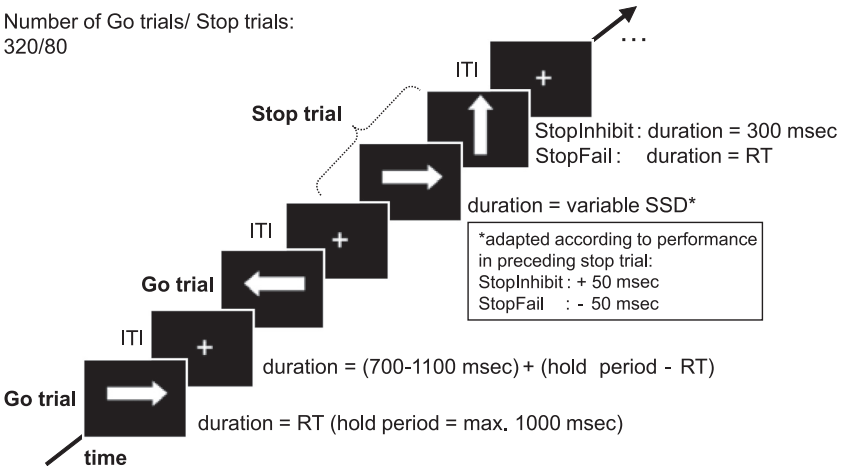

Figure 2. Timing of the SST. In go trials, the go stimulus was displayed until a response was recorded but for a maximum of 1000 msec. In stop trials, the go stimulus was presented for the duration of the variable stop-signal delay (SSD) (mean ± SD: alcohol = 184 msec ± 91; placebo = 196 msec ± 85) followed by the stop-signal for 300 msec 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 intertrial interval (ITI) (mean = 900 msec). In stop trials, the SSD (initial SSD = 200 msec) was adapted dynamically according to the performance in the preceding stop trial (25): if participants successfully inhibited the response, the SSD was increased by 50 msec; if they failed to inhibit the response, the SSD was decreased by 50 msec. The SST lasted for 13 min. RT, reaction time; other abbreviations as in Figure 1.

fMRI Alcohol Clamping. For behavioral data analysis, 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 used paired *t* tests to compare alcohol with placebo responses and computed alcohol-induced impairment of inhibitory control ($SSRT_{alcohol}$–$SSRT_{placebo}$) for additional analyses.

On the first level of fMRI data analysis, 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 with a general linear model. Realignment parameters were included as nuisance variables (3 translation, 3 rotation parameters) (for Preprocessing, see Supplement 1). Correct go trials were represented within the implicit baseline of the general linear model (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 sec). 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 msec. Because 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 the canonical hemodynamic response function of SPM8. We corrected for serial auto-correlations with an autoregressive AR(1) model implemented in SPM 8.

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 inferior frontal gyri, 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 because 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 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 (for inhibition-related areas affected by alcohol) perfusion measured before the SST (see ASL data-analysis in Supplement 1) and assessed alcohol effects on perfusion with 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 in Supplement 1) with AMOS 21 (IBM).

fMRI Alcohol Clamping 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 might be biased by unspecific exploratory behavior (43,45). This was supported by the finding that drinks/drinking day assessed by a time-line follow-back interview (48) correlated significantly 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. The 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 Results, Between-Subject Variables in Supplement 1). Thus, we did not include those covariates in 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 msec, whereas 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). The 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 with StopFail (Figure 3, Table 2B). In contrast, StopFail increased brain responses in bilateral precentral gyri and anterior insulae, medial frontal, temporal, and motor-related brain areas compared with StopInhibit (Figure 3, Table 2C).

Alcohol effects on inhibition-related brain responses. The whole-brain conjunction analysis of "alcohol<placebo," StopInhibit, and

Table 1. Effects of Alcohol on Behavioral SST Outcome Variables During fMRI Alcohol Clamping

	Placebo		Alcohol		Test-Statistics
	Mean	(SEM)	Mean	(SEM)	Placebo vs. Alcohol
SSRT (msec)[a]	207.6	(6.3)	226.0	(8.1)	$t_{41} = -4.07$, $p < .001$
Probability of Inhibition (%)[b]	48.2	(.5)	46.2	(.8)	$t_{41} = 2.97$, $p = .005$
Mean Go RT (msec)[c]	414.9	(9.6)	419.1	(10.0)	$t_{41} = -.88$, $p = .383$
Correct Go Trials (%)[b]	96.9	(.4)	95.5	(.5)	$t_{41} = 3.35$, $p = .002$

Alcohol and placebo responses were compared with paired *t* tests (*t*).
fMRI, functional magnetic resonance imaging; RT, reaction time; SSRT, stop-signal reaction time; SST, stop-signal task.
[a] $p < .001$.
[b] $p < .01$.
[c] p = nonsignificant.

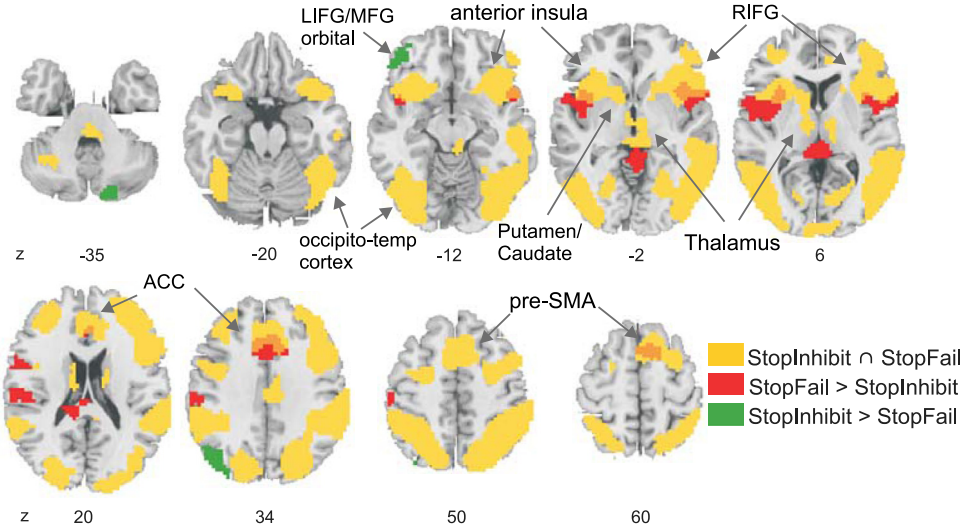

Figure 3. Activation of the fronto-subcortical motor inhibition network and bilateral occipito-temporo-parietal cortex during stop trials. Brain areas that were active across both stopping conditions (conjunction of StopInhibit and StopFail) are shown in yellow. Increased brain activation for StopInhibit 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. ACC, anterior cingulate cortex; LIFG, left inferior frontal gyrus; MFG, middle frontal gyrus; pre-SMA, pre-supplementary motor area; RIFG, right inferior frontal gyrus.

StopFail revealed that alcohol decreased inhibition-related brain responses in two clusters: the RIFG/anterior insula; and the right middle occipito-temporal cortex (Figure 4A–C, Table 2D). Furthermore, no brain area showed increased inhibitory activation under alcohol (vs. placebo), and no interaction between stopping and drug emerged, indicating that alcohol effects did not differ between stopping conditions (Table S2 in Supplement 1).

Association of Alcohol Effects on Regional Inhibition-Related Brain Responses and Inhibitory Control. For regional analyses, we extracted mean brain responses for the RIFG/insula and occipito-temporal cortex (Figure 4B,C) and collapsed alcohol effects across stopping conditions ($[\text{StopInhibit}+\text{StopFail}]_{\text{alcohol}} - [\text{StopInhibit}+\text{StopFail}]_{\text{placebo}}$). 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 alpha-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 (Table S3 in Supplement 1). Path analyses for the RIFG/insula and occipito-temporal cortex showed that perfusion alcohol effects did neither significantly influence alcohol effects on inhibition-related BOLD responses nor on inhibitory control (Figure S2, Table S4 in Supplement 1). 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).

fMRI Alcohol Clamping 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 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 occipito-temporal 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 been linked not only 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 (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 (22).

Larger decreases of inhibition-related brain responses in the RIFG/insula and the occipito-temporal cortex under alcohol were linked to more pronounced alcohol-induced impairment of inhibitory control. Previously, decreased activation of the RIFG was found to be related to low inhibitory control measured both in a sober state (18,2129-31) and under the influence of alcohol

Table 2. Results from the 2 (Stopping: StopInhibit, StopFail) × 2 (Drug: Alcohol, Placebo) Full-Factorial fMRI Analysis

			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	< .001	3253	< .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	< .001	4804	< .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	< .001	4088	< .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	< .001	1138	< .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	< .001	457	< .001	6.15
L	MFG	10	−33	50	19				5.90
L	MFG	6	−24	−4	49	< .001	422	< .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	.001	168	< .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	.141	51	.035	4.86
L	MFG	11	−45	44	−11	.062	69	.166	4.41
L	IFG	47	−51	38	−14			.362	4.14
L	IFG	47	−36	32	−17			.949	3.51
L	MOG	19	−36	−82	40	.008	118	.341	4.17
L	Angular G	39	−45	−76	28			.669	3.86
L	SOG	19	−36	−85	31			.906	3.59
(C) StopFail > StopInhibit									
L	Precentral G	6	−57	5	13	< .001	417	.001	5.68
L	Insula	—	−36	8	4			.034	4.86
L	STG	22	−57	−7	7			.976	3.42
L	Postcentral G	43	−63	−19	22	.001	191	.003	5.44
L	Precentral G	4	−60	−22	43			.078	4.64
R	Insula	13	45	11	−2	< .001	251	.007	5.26
R	Precentral G	44	48	2	10			.121	4.51
R	STG	22	60	8	4			.213	4.33
L	Cingulate G	32	−6	20	34	< .001	205	.008	5.23
L	ACC	24	0	29	25			.719	3.81
	Cerebellum	—	0	−31	10	< .001	205	.165	4.42
L	Culmen	—	0	−43	−2			.353	4.15
L	Pulvinar	—	−12	−37	16			.525	3.99
R	SMA	6	9	11	61	.148	50	.209	4.34
(D) Alcohol<Placebo in Inhibition-Related Brain Areas (Conjunction of alcohol<placebo, StopInhibit, and StopFail)									
R	IFG	45	36	26	7	.015	103	.103	4.56
R	Insula	—	33	14	7			.14	4.47
R	IFG	47	51	20	1			.773	3.76
R	MTG	21	57	−52	4	.056	71	.372	4.13
R	MTG	21	66	−49	4			.95	3.51
R	MOG	37	51	−70	1			.994	3.3

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 with placebo. The *p* values corrected for multiple comparisons (family-wise error [FWE] at cluster and peak level), *t* values, and Montreal Neurological Institute (MNI) coordinates are shown. Whole-brain significance threshold: $p < .001$ (uncorrected) with at least 50 connected voxels.

ACC, anterior cingulate cortex; BA, Brodmann area; corr., corrected; G, gyrus; IFG, inferior frontal gyrus; IPL, inferior parietal lobe; ITG, inferior temporal gyrus; L, left; MOG, middle occipital gyrus; MTG, middle temporal gyrus; Post., posterior; R, right; SOG, superior occiptal gyrus; SMA, supplementary motor area; STG, superior temporal gyrus.

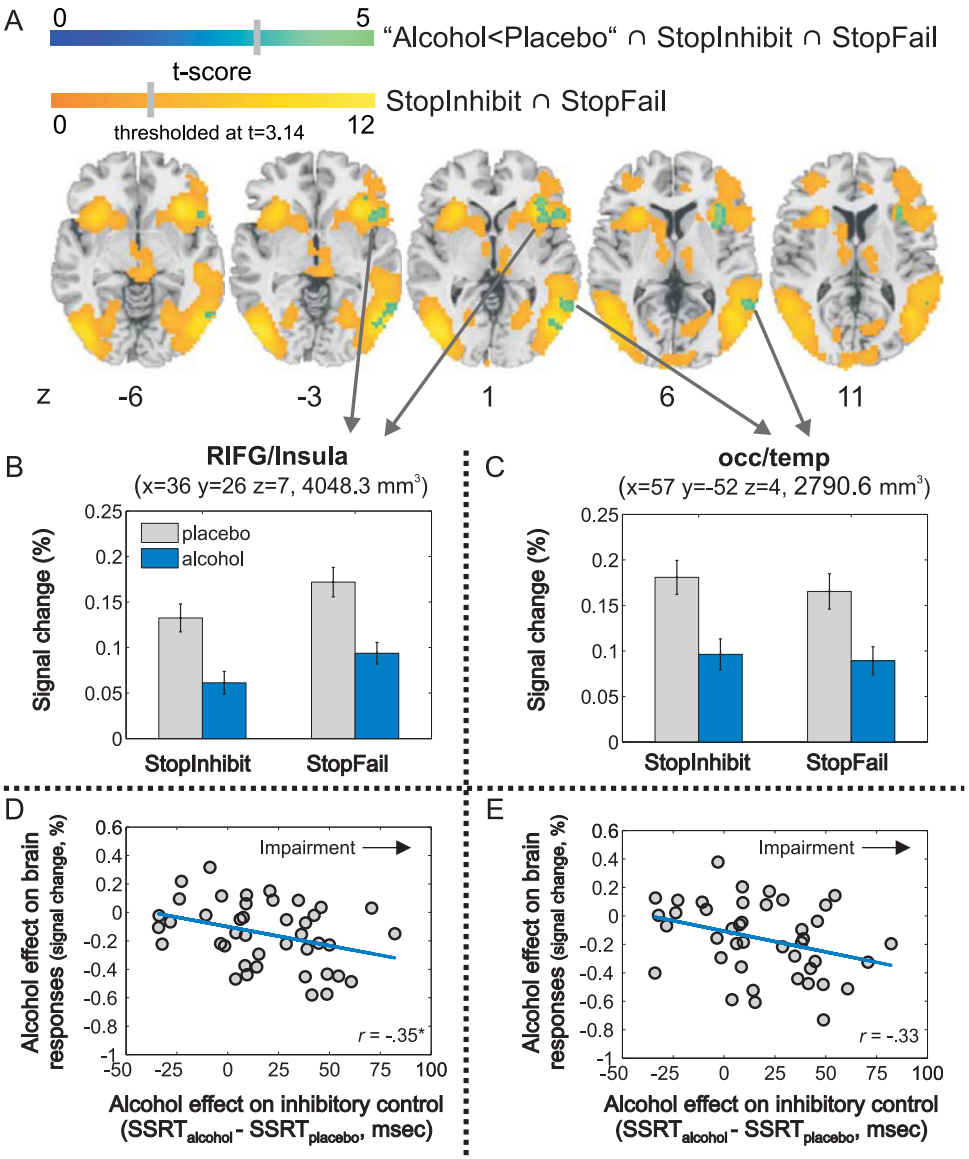

Figure 4. Whole-brain conjunction analysis. **(A)** Alcohol effects (alcohol<placebo) on inhibition-related brain responses (StopInhibit ∩ StopFail). Brain maps showing the alcohol effect (blue color scale) are overlaid on inhibition-related brain responses (yellow-orange color scale; significance threshold: $p < .001$ 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: right inferior frontal gyrus (RIFG)/insula **(B)**; and the occipito-temporal cortex (occ/temp) **(C)**. Regional analyses: correlation between alcohol-induced impairment of inhibitory control (stop-signal reaction time $[SSRT]_{alcohol}–SSRT_{placebo}$; > 0: impaired; < 0: improved) and alcohol effects on regional inhibition-related brain responses in the RIFG/insula **(D)**; and the occipito-temporal cortex (occ/temp) **(E)**. Error bars represent the SEM. Locations are given in Montreal Neurological Institute space. *$p < .025$ (alpha-level corrected for multiple testing, $p = .05$/[number of tests = 2]). *r*, Pearson correlation coefficient.

(18). While alcohol decreased inhibition-related activation in the anterior portion of the RIFG in negative FHA people only, a higher risk for alcoholism in positive FHA participants was linked to less neural reactivity to alcohol (18). Compared with 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 with placebo. Noteworthy, FHA affected neither behavioral nor neural alcohol effects in our study, which could be due to 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 that are present in both conditions and precede motor inhibition. We do not assume that alcohol impaired the attention capacity in general, because the mean Go RT was not affected by alcohol (6). Our results underline that during inhibitory control alcohol affects cognitive control processes indicated by decreased brain responses in prefrontal areas (15,16,18) and not directly motor inhibition associated with subcortical areas and the pre-SMA (26,27).

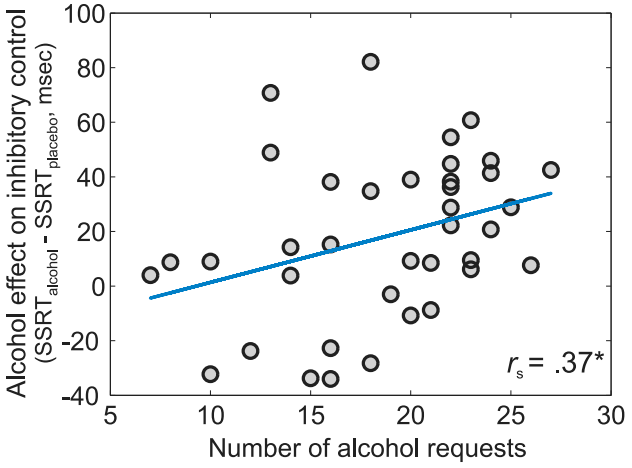

Figure 5. Correlation between alcohol-induced impairment of inhibitory control at .6 g/kg during functional magnetic resonance imaging alcohol clamping and number of alcohol requests during free-access alcohol self-administration ($n = 38$, valid free-access data). *$p < .05$. r_s, Spearman correlation coefficient; SSRT, stop-signal reaction time.

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" (Supplement 1) with the predictors $SSRT_{placebo}$, subjective perceptions of alcohol, and saccadic latency [variables significantly affected by alcohol (56–58)] (see Level of Alcohol Intoxication and Tables S5 and S6 in Supplement 1). 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 due to the finding that alcohol affected fronto-temporal and not stopping-related pre-motor and subcortical areas. To further explore whether alcohol also affects stopping-related areas and whether 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 of approximately .9 g/kg) and in real life (Table S1 in Supplement 1), 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 might 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 and Table S4 in Supplement 1). Increased perfusion under alcohol did neither significantly influence 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, although 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 estimation of changes in the metabolic rate of oxygen. For reasons of experimental complexity, we did not measure heart rate, respiration, and blood pressure, which might also have contributed to disentangle cardiovascular from neural alcohol effects.

Conclusions

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 might 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).

We will test in the same participants, at the age of 21, whether alcohol-related impairment of inhibitory control and attenuated inhibition-related brain responses can predict free-access alcohol consumption that might have escalated in some and went back to normal in others. Furthermore, 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.

This research was done in collaboration with Professor Sean O'Connor (Indiana University School of Medicine) and was supported by the National Institute on Alcohol Abuse and Alcoholism (Grant No. U01AA017900), the Bundesministerium für Bildung und Forschung (BMBF Grant No. 01EV0711), and the Deutsche Forschungsgemeinschaft (DFG FOR 1617 [Grant No. SM 80/7-1, ZI 1119/4-1], and SFB 940).

We thank Victor Vitvitsky for adjusting the computer-assisted alcohol infusion systems software to the German settings; the staff at the Neuroimaging Centre Dresden for managing MRI recordings; Marie-Charlott Randhan and Christine Markert for help during data acquisition; Dr. Inge Mick, Alexandra Markovic, and Christian Seipt for recruitment and data acquisition of the free-access alcohol self-administration part; Dr. Nils B. Kroemer for statistical advice; and the Center for Information Services and High Performance Computing (ZIH) at TU Dresden for cluster-computing time.

The authors declare that over the past three years, USZ has received compensation from sächsische Landesärztekammer, Gewerkschaft Erziehung und Wissenschaft, Park-Krankenhaus Leipzig, ABW Wissenschaftsverlag, Servier, Janssen, and Lundbeck. All other authors report no biomedical financial interests or potential conflicts of interest.

ClinicalTrials.gov: Collaboration on Alcohol Self Administration in Adolescents and Young Adults—Specific Aim 2: To Examine the

Effect of Acute Alcohol Administration on Forebrain Disinhibition Using Functional Magnetic Resonance Imaging (fMRI); http://clinicaltrial.gov/ct2/show/NCT01097213?term=NCT01097213&rank=1; NCT01097213.

Supplementary material cited in this article is available online at http://dx.doi.org/10.1016/j.biopsych.2013.12.017.

1. Corte CM, Sommers MS (2005): Alcohol and risky behaviors. *Annu Rev Nurs Res* 23:327–360.
2. Halpern-Felsher BL, Millstein SG, Ellen JM (1996): Relationship of alcohol use and risky sexual behavior: A review and analysis of findings. *J Adolesc Health* 19:331–336.
3. Gilman JM, Smith AR, Ramchandani VA, Momenan R, Hommer DW (2012): The effect of intravenous alcohol on the neural correlates of risky decision making in healthy social drinkers. *Addict Biol* 17: 465–478.
4. Giancola PR, Parrott DJ (2008): Further evidence for the validity of the Taylor Aggression Paradigm. *Aggress Behav* 34:214–229.
5. Hoaken PN, Pihl RO (2000): The effects of alcohol intoxication on aggressive responses in men and women. *Alcohol Alcohol* 35: 471–477.
6. de Wit H, Crean J, Richards JB (2000): Effects of d-amphetamine and ethanol on a measure of behavioral inhibition in humans. *Behav Neurosci* 114:830–837.
7. Loeber S, Duka T (2009): Acute alcohol impairs conditioning of a behavioural reward-seeking response and inhibitory control processes —implications for addictive disorders. *Addiction* 104:2013–2022.
8. Mulvihill LE, Skilling TA, Vogel-Sprott M (1997): Alcohol and the ability to inhibit behavior in men and women. *J Stud Alcohol* 58: 600–605.
9. Feola TW, de Wit H, Richards JB (2000): Effects of d-amphetamine and alcohol on a measure of behavioral inhibition in rats. *Behav Neurosci* 114:838–848.
10. Marczinski CA, Abroms BD, Van Selst M, Fillmore MT (2005): Alcohol-induced impairment of behavioral control: Differential effects on engaging vs. disengaging responses. *Psychopharmacology (Berl)* 182: 452–459.
11. Fillmore MT, Weafer J (2004): Alcohol impairment of behavior in men and women. *Addiction* 99:1237–1246.
12. Field M, Wiers RW, Christiansen P, Fillmore MT, Verster JC (2010): Acute alcohol effects on inhibitory control and implicit cognition: Implications for loss of control over drinking. *Alcohol Clin Exp Res* 34: 1346–1352.
13. Weafer J, Fillmore MT (2008): Individual differences in acute alcohol impairment of inhibitory control predict ad libitum alcohol consumption. *Psychopharmacology (Berl)* 201:315–324.
14. Marczinski CA, Combs SW, Fillmore MT (2007): Increased sensitivity to the disinhibiting effects of alcohol in binge drinkers. *Psychol Addict Behav* 21:346–354.
15. Anderson BM, Stevens MC, Meda SA, Jordan K, Calhoun VD, Pearlson GD (2011): Functional imaging of cognitive control during acute alcohol intoxication. *Alcohol Clin Exp Res* 35:156–165.
16. Marinkovic K, Rickenbacher E, Azma S, Artsy E (2012): Acute alcohol intoxication impairs top-down regulation of Stroop incongruity as revealed by blood oxygen level-dependent functional magnetic resonance imaging. *Hum Brain Mapp* 33:319–333.
17. Schuckit MA, Tapert S, Matthews SC, Paulus MP, Tolentino NJ, Smith TL, *et al.* (2012): fMRI differences between subjects with low and high responses to alcohol during a stop signal task. *Alcohol Clin Exp Res* 36: 130–140.
18. Kareken DA, Dzemidzic M, Wetherill L, Eiler W, Oberlin BG, Harezlak J, *et al.* (2013): Family history of alcoholism interacts with alcohol to affect brain regions involved in behavioral inhibition. *Psychopharmacology (Berl)* 228:335–345.
19. Swick D, Ashley V, Turken U (2011): Are the neural correlates of stopping and not going identical? Quantitative meta-analysis of two response inhibition tasks. *Neuroimage* 56:1655–1665.
20. Aron AR, Poldrack RA (2006): Cortical and subcortical contributions to Stop signal response inhibition: Role of the subthalamic nucleus. *J Neurosci* 26:2424–2433.
21. Aron AR, Behrens TE, Smith S, Frank MJ, Poldrack RA (2007): Triangulating a cognitive control network using diffusion-weighted magnetic resonance imaging (MRI) and functional MRI. *J Neurosci* 27:3743–3752.
22. Boehler CN, Appelbaum LG, Krebs RM, Hopf JM, Woldorff MG (2010): Pinning down response inhibition in the brain—conjunction analyses of the stop-signal task. *Neuroimage* 52:1621–1632.
23. Levy BJ, Wagner AD (2011): Cognitive control and right ventrolateral prefrontal cortex: Reflexive reorienting, motor inhibition, and action updating. *Ann N Y Acad Sci* 1224:40–62.
24. Rubia K, Smith AB, Brammer MJ, Taylor E (2003): Right inferior prefrontal cortex mediates response inhibition while mesial prefrontal cortex is responsible for error detection. *Neuroimage* 20:351–358.
25. Logan GD, Schachar RJ, Tannock R (1997): Impulsivity and inhibitory control. *Psychol Sci* 8:60–64.
26. Sharp DJ, Bonnelle V, De B,X, Beckmann CF, James SG, Patel MC, *et al.* (2010): Distinct frontal systems for response inhibition, attentional capture, and error processing. *Proc Natl Acad Sci U S A* 107:6106–6111.
27. Duann JR, Ide JS, Luo X, Li CS (2009): Functional connectivity delineates distinct roles of the inferior frontal cortex and presupplementary motor area in stop signal inhibition. *J Neurosci* 29:10171–10179.
28. Verbruggen F, Aron AR, Stevens MA, Chambers CD (2010): Theta burst stimulation dissociates attention and action updating in human inferior frontal cortex. *Proc Natl Acad Sci U S A* 107:13966–13971.
29. Whelan R, Conrod PJ, Poline JB, Lourdusamy A, Banaschewski T, Barker GJ, *et al.* (2012): Adolescent impulsivity phenotypes characterized by distinct brain networks. *Nat Neurosci* 15:920–U153.
30. Rubia K, Smith AB, Brammer MJ, Toone B, Taylor E (2005): Abnormal brain activation during inhibition and error detection in medication-naive adolescents with ADHD. *Am J Psychiatry* 162:1067–1075.
31. Rubia K, Smith AB, Taylor E, Brammer M (2007): Linear age-correlated functional development of right inferior fronto-striato-cerebellar networks during response inhibition and anterior cingulate during error-related processes. *Hum Brain Mapp* 28:1163–1177.
32. Chamberlain SR, Hampshire A, Muller U, Rubia K, Del Campo N, Craig K, *et al.* (2009): Atomoxetine modulates right inferior frontal activation during inhibitory control: A pharmacological functional magnetic resonance imaging study. *Biol Psychiatry* 65:550–555.
33. Jacobson L, Javitt DC, Lavidor M (2011): Activation of inhibition: Diminishing impulsive behavior by direct current stimulation over the inferior frontal gyrus. *J Cogn Neurosci* 23:3380–3387.
34. Palmer RH, Young SE, Hopfer CJ, Corley RP, Stallings MC, Crowley TJ, *et al.* (2009): Developmental epidemiology of drug use and abuse in adolescence and young adulthood: Evidence of generalized risk. *Drug Alcohol Depend* 102:78–87.
35. Grant JD, Scherrer JF, Lynskey MT, Lyons MJ, Eisen SA, Tsuang MT, *et al.* (2006): Adolescent alcohol use is a risk factor for adult alcohol and drug dependence: Evidence from a twin design. *Psychol Med* 36: 109–118.
36. McCambridge J, McAlaney J, Rowe R (2011): Adult consequences of late adolescent alcohol consumption: A systematic review of cohort studies. *PLoS Med* 8:e1000413.
37. Wiesner M, Weichold K, Silbereisen RK (2007): Trajectories of alcohol use among adolescent boys and girls: Identification, validation, and sociodemographic characteristics. *Psychol Addict Behav* 21:62–75.
38. Williams BR, Ponesse JS, Schachar RJ, Logan GD, Tannock R (1999): Development of inhibitory control across the life span. *Dev Psychol* 35: 205–213.
39. Gunther M, Oshio K, Feinberg DA (2005): Single-shot 3D imaging techniques improve arterial spin labeling perfusion measurements. *Magn Reson Med* 54:491–498.
40. Khalili-Mahani N, van Osch MJ, Baerends E, Soeter RP, de Kam M, Zoethout RW, *et al.* (2011): Pseudocontinuous arterial spin labeling reveals dissociable effects of morphine and alcohol on regional cerebral blood flow. *J Cereb Blood Flow Metab* 31:1321–1333.
41. Volkow ND, Mullani N, Gould L, Adler SS, Guynn RW, Overall JE, *et al.* (1988): Effects of acute alcohol intoxication on cerebral blood flow measured with PET. *Psychiatry Res* 24:201–209.
42. Wise RG, Tracey I (2006): The role of fMRI in drug discovery. *J Magn Reson Imaging* 23:862–876.
43. Zimmermann US, Mick I, Laucht M, Vitvitskiy V, Plawecki MH, Mann KF, *et al.* (2009): Offspring of parents with an alcohol use disorder prefer higher levels of brain alcohol exposure in experiments involving

computer-assisted self-infusion of ethanol (CASE). *Psychopharmacology (Berl)* 202:689–697.
44. O'Connor S, Morzorati S, Christian J, Li TK (1998): Clamping breath alcohol concentration reduces experimental variance: Application to the study of acute tolerance to alcohol and alcohol elimination rate. *Alcohol Clin Exp Res* 22:202–210.
45. Zimmermann US, Mick I, Vitvitskyi V, Plawecki MH, Mann KF, O'Connor S (2008): Development and pilot validation of computer-assisted self-infusion of ethanol (CASE): A new method to study alcohol self-administration in humans. *Alcohol Clin Exp Res* 32:1321–1328.
46. Ridderinkhof KR, Band GPH, Logan GD (1999): A study of adaptive behavior: Effects of age and irrelevant information on the ability to inhibit one's actions. *Acta Psychol* 101:315–337.
47. Verbruggen F, Logan GD (2009): Models of response inhibition in the stop-signal and stop-change paradigms. *Neurosci Biobehav Rev* 33:647–661.
48. Sobell LC, Maisto SA, Sobell MB, Cooper AM (1979): Reliability of alcohol abusers' self-reports of drinking behavior. *Behav Res Ther* 17:157–160.
49. Corbetta M, Shulman GL (2002): Control of goal-directed and stimulus-driven attention in the brain. *Nat Rev Neurosci* 3:201–215.
50. Corbetta M, Patel G, Shulman GL (2008): The reorienting system of the human brain: From environment to theory of mind. *Neuron* 58:306–324.
51. Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, *et al.* (2007): Dissociable intrinsic connectivity networks for salience processing and executive control. *J Neurosci* 27:2349–2356.
52. Dosenbach NU, Visscher KM, Palmer ED, Miezin FM, Wenger KK, Kang HC, *et al.* (2006): A core system for the implementation of task sets. *Neuron* 50:799–812.
53. Hester R, Fassbender C, Garavan H (2004): Individual differences in error processing: A review and reanalysis of three event-related fMRI studies using the GO/NOGO task. *Cereb Cortex* 14:986–994.
54. Ullsperger M, von Cramon DY (2004): Neuroimaging of performance monitoring: Error detection and beyond. *Cortex* 40:593–604.
55. Stevens MC, Kiehl KA, Pearlson GD, Calhoun VD (2009): Brain network dynamics during error commission. *Hum Brain Mapp* 30:24–37.
56. King AC, de Wit H, McNamara PJ, Cao D (2011): Rewarding, stimulant, and sedative alcohol responses and relationship to future binge drinking. *Arch Gen Psychiatry* 68:389–399.
57. Jantti V, Lang AH, Keskinen E, Lehtinen I, Pakkanen A (1983): Acute effects of intravenously given alcohol on saccadic eye movements and subjective evaluations of intoxication. *Psychopharmacology* 79: 251–255.
58. Ramchandani VA, O'Connor S, Blekher T, Kareken D, Morzorati S, Nurnberger J Jr., *et al.* (1999): A preliminary study of acute responses to clamped alcohol concentration and family history of alcoholism. *Alcohol Clin Exp Res* 23:1320–1330.
59. Leontiev O, Buxton RB (2007): Reproducibility of BOLD, perfusion, and CMRO2 measurements with calibrated-BOLD fMRI. *Neuroimage* 35: 175–184.
60. Hoge RD, Atkinson J, Gill B, Crelier GR, Marrett S, Pike GB (1999): Investigation of BOLD signal dependence on cerebral blood flow and oxygen consumption: The deoxyhemoglobin dilution model. *Magn Reson Med* 42:849–863.
61. Pike GB (2012): Quantitative functional MRI: Concepts, issues and future challenges. *Neuroimage* 62:1234–1240.