

Alcohol-related context modulates neural correlates of inhibitory control in alcohol dependent patients: Preliminary data from an fMRI study using an alcohol-related Go/NoGo-task

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ABSTRACT

Alcohol use disorder (AUD) is characterized by both impaired inhibitory control and heightened cue reactivity, including enhanced craving and drinking urges in response to alcohol-related stimuli. The interaction between these two mechanisms is thought to be crucial in the maintenance of addiction and relapse. The present study used a newly developed alcohol-related Go/NoGo-task to investigate how exposure to alcohol-related cues affects neural processing of inhibitory control in subjects with AUD.

Functional magnetic resonance imaging (fMRI) was recorded during performance of a Go/NoGo task, which incorporated alcohol-related and neutral stimuli as Go and NoGo trials in abstinent AUD patients and healthy controls (HC).

AUD patients exhibited increased activation of a fronto-striatal-parietal network during successful response inhibition relative to HC. Within the AUD group, activation for alcohol-related (relative to neutral) inhibition was enhanced in regions including bilateral anterior cingulate cortex (ACC), right medial frontal and precentral gyri, and right putamen. Activation differences in the right ACC increased with subjective craving.

These preliminary findings suggest that AUD patients need to recruit enhanced neuronal resources for successful inhibition. In parts of the inhibitory network, this hyperactivation is enhanced when inhibition takes place in an alcohol-related context. Activation in the ACC increased stronger in patients experiencing high craving, possibly because of an enhanced conflict.

The task introduced here thus allows to investigate neural processing of alcohol-related inhibition in an AUD sample. The preliminary results suggest that exposure to alcohol-related cues intensifies the demand on an already challenged inhibitory system in recently abstinent patients with AUD.

1. Introduction

Alcohol is the most frequently used psychoactive drug worldwide and chronic problematic alcohol use results in severe neurological, medical, psychological, and social damage [1]. Moreover, chronic harmful alcohol use has come to be viewed as a complex alteration of brain processes in which the imbalance between heightened cue reactivity for alcohol-related stimuli and impaired inhibitory control is considered to be crucial [2–6]. Unfortunately, these two mechanisms

have mostly been studied separately on a neurophysiological level. As such, their mutual interplay is not well understood. The present study aimed to investigate how individual levels of craving and exposure to alcohol-related stimuli affects neural correlates of inhibitory control in subjects with alcohol use disorder (AUD).

Inhibitory control and performance monitoring are highly relevant to addictive behaviors [7–9]. By monitoring performance and inhibiting habitual behaviors, cognitive control allows one to maneuver changing environments and optimizes goal-directed actions [10]. Moreover,

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impaired cognitive control in AUD subjects is considered to be both a determinant and a consequence of addictive behaviors [10], and thereby contributes to difficulty in maintaining abstinence [11]. Another central concept in the current understanding of AUD is alcohol-cue reactivity [3, 12,13]. It is thought to originate from classical conditioning during long-term problematic alcohol use [14] and can be assessed on behavioral, (neuro)physiological, and subjective levels. On a neurophysiological level, it is described as an enhanced reaction to alcohol-related cues, mostly in networks related to salience attribution and reward prediction [6]. On a subjective level, exposure to cues associated with alcohol consumption can elicit conditioned urges to drink alcohol (cue-elicited craving [14,15]). Taken together, the current neuroscientific view of AUD holds that already diminished inhibitory control processes have to compete with alcohol-related cue-reactivity, including neurophysiological reactions and craving, when it comes to the inhibition of drinking behavior in high-risk situations (e.g [5,6,16]).

A common way to investigate inhibitory control processes is the Go/NoGo task [17]. During this task, a continuous series of stimuli that require a response (Go stimuli) are interrupted by stimuli requiring inhibition of the prepotent responses (NoGo stimuli [17,18]). Typically, the percentage of NoGo stimuli is low to increase the inhibitory effort necessary to successfully withhold a response [19], thus providing a useful way to investigate inhibitory control processes and their underlying cortical activity [20]. On a behavioral level, meta-analyses summarize evidence for impaired inhibitory control in AUD [21–23]. Also, the behavioral inhibitory control deficits seem to be pronounced when alcohol-associated stimuli are presented [8,16]. On a neurophysiological level, convergent findings from functional magnetic resonance imaging (fMRI) studies indicate that response inhibition in healthy individuals is mediated by a mainly right lateralized fronto-striatal-parietal network, including the inferior frontal gyrus (IFG), dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), pre-supplementary motor area (SMA), subcortical areas (thalamus/basal ganglia), and the inferior parietal cortex [20,24]. In AUD and other substance use disorders (SUD), meta-analyses revealed dysregulated neural activity in a fronto-striatal-parietal network during response inhibition compared to healthy control subjects [11,17]. The precise localization and direction (hypo-activity or hyper-activity) of this dysregulated activation is still unclear. Potential reasons for this inconsistency are differences in length of sobriety, severity and quantity of use, task difficulty, analysis method, type of task, and concurrent medications [11,17]. On one hand, some studies have linked successful response inhibition to decreased inhibition-related neural activity in structures of the inhibitory control network in AUD [25] and SUD [19, 26] or showed inconsistent results [27]. On the other hand, there is growing evidence of increased inhibition-related neural activity in addictive disorders, at least when participants showed comparable task performance during fMRI scanning. This hyperactivation has been observed in the DLPFC, orbitofrontal cortex, posterior and anterior cingulate gyri, basal ganglia, and parietal structures [18,28–33] and has been interpreted as functional compensation whereby the inhibitory control network recruits enhanced resources to successfully inhibit responses [29].

While the vast majority of these fMRI studies investigated inhibition in a neutral context, the investigation of alcohol-specific inhibition in AUD on a neurophysiological level is rare, with the exception of very few studies using multi-channel electroencephalography (EEG; Petit et al., 2014; [34]) or fMRI [18,33].

To the best of our knowledge, there have been only two fMRI studies using alcohol-related cues in a Go/NoGo task to investigate the neural activity associated with response inhibition in an alcohol related context. Czapla et al. [33] reported that successful response inhibition in an alcohol-related context was reflected by enhanced activation in the lingual gyrus, middle occipital gyrus, and superior occipital gyrus in AUD patients compared to healthy controls (HC). Ames et al. [18] reported enhanced BOLD activation in the DLPFC, ACC, and right anterior

insula during alcohol-related NoGo trials for heavy drinkers compared to light drinkers. However, both studies used alcohol-related stimuli exclusively as NoGo trials and contrasted them with non-alcoholic Go stimuli, thus limiting the possibility to disentangle effects of stimulus type from effects due to context-dependent inhibition. A design with alcohol-related and neutral stimuli in both conditions (Go and NoGo) has not yet been applied in fMRI investigations and could help elucidate how exposure to an alcohol-related context affects the neural correlates of inhibitory control.

In the present study, fMRI was recorded in AUD subjects and healthy controls during performance of a newly developed Go/NoGo task incorporating alcohol-related and neutral stimuli in both the Go- and NoGo-conditions, thus allowing the assessment of response inhibition in both alcohol-related and neutral contexts. This experimental design is suited to investigate the effect of an alcohol-related context on inhibitory control, thus precisely targeting the imbalance that is central to current neuroscientific conceptualizations of addiction [6,35].

Driven by the understanding that the capability to exert inhibitory control in the presence of salient alcohol-related stimuli is crucial to prevent relapse, the focus of the present study was to investigate successful inhibition in an alcohol-related context in patients with AUD. To focus on this precise type of inhibition, we set out to first subtract activation during alcohol-related Go trials from activation during alcohol-related NoGo trials. Then we compared this difference to the respective difference in neutral trials. Reflecting on the idea that an alcohol-related context might enhance conflict between the urge to react to a salient stimulus and the task-inherent request to inhibit a response, we hypothesized that successful inhibition of alcohol-related NoGo trials requires additional neuronal resources in AUD patients by enhancing demands on and activation of the inhibitory control network, which comprises the IFG, dorsolateral and medial prefrontal cortex, anterior and posterior cingulate cortex (ACC, PCC), (Pre-)SMA and premotor cortex, subcortical areas (Putamen, Thalamus), and inferior parietal cortex [20,24,28,29].

Furthermore, we assumed that these enhanced demands on the inhibitory network intensify with increased craving. This effect is expected particularly in the ACC, which is involved in conflict monitoring [36], or in the PCC, which is involved in strategy updating in individually salient contexts [37,38], and has been suggested to generate electrophysiological effects related to the interaction of craving and alcohol-specific inhibition [34]. Therefore, the association between neuronal ACC and PCC activation reflecting alcohol-related inhibition and subjectively experienced craving was also examined.

2. Materials and methods

2.1. Participants

The study protocol was approved by the Ethics Committee of the Canton Bern, Bern, Switzerland (Proposal Nr.: 12/06). All subjects gave written informed consent prior to inclusion. Fifteen subjects were inpatients with AUD and were recruited during a residential alcohol relapse prevention program at the University Hospital of Psychiatry in Bern. All patients were diagnosed with alcohol dependence according to the 10th revision of the International Statistical Classification of Diseases (ICD-10, World Health Organization, 1993). The patients were required to be detoxified and were abstinent for a minimum of 8 days. Reasons for exclusion were: any history of neurological disorders, primary psychiatric illnesses (e.g. depression, anxiety/personality disorder), or multiple use disorders (except nicotine). Additionally, fifteen healthy controls were recruited in the social surroundings of students of the University of Bern or via flyers, while care was taken that healthy controls were not confined to an academic sample. Reasons for exclusion of healthy controls were: any history of substance use disorders, neurological disorders, or primary psychiatric illnesses (e.g. depression, anxiety/personality disorder).

Three participants (2 AUD patients, 1 healthy control) were excluded from data analysis due to too many errors on Go trials (1) and technical problems during fMRI scanning (2), which left a total of 27 subjects for this study. Following these exclusions, the final groups consisted of 13 AUD patients and 14 HC.

2.2. Questionnaires

The German version of the Obsessive-Compulsive Drinking Scale (OCDS, [39]) was used to assess participants' subjective craving, yielding an overall score (OCDS-overall, OCDS-O) as well as subscales for behavioral (OCDS-compulsions, OCDS-C) and cognitive aspects of craving (OCDS-thoughts, OCDS-T). AUD patients completed the OCDS with respect to the week before admission to the hospital and control subjects with respect to the week before study participation. Because the behavioral component of craving was deemed most relevant for a motor

inhibition paradigm, the behavioral subscale (OCDS-C), which measures drinking urges, was used to operationalize craving in the present study and was thus introduced as a primary predictor in the fMRI analyses.

Additionally, three questionnaires were used in the control group to exclude controls with psychopathological symptoms and problematic drinking habits. The global severity index of the Brief Symptom Inventory (BSI, German version; [40]; cut-off value: 63) and the Hamilton Depression Scale (HAMD, [41]; cut-off value: 13) were used to assess psychopathological symptoms. The Alcohol Use Disorder Identification Test (Audit, [42], cut-off value: 8) was used to assess participants with potentially problematic drinking behavior.

2.3. Go/NoGo task

During fMRI Scanning, participants completed a Go/NoGo task (see Fig. 1 in supplementary online material) with pictures of either alcohol-

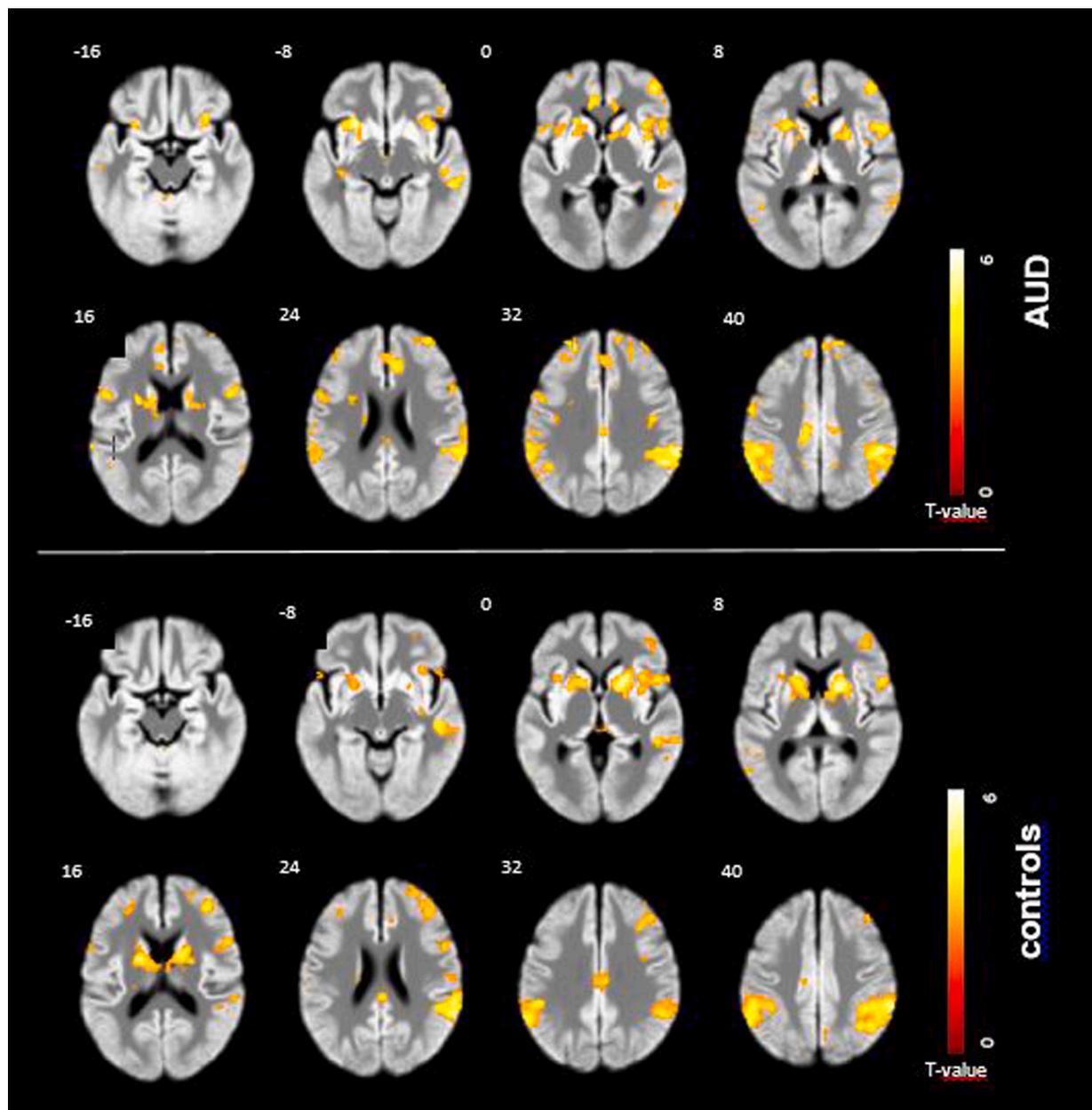


Fig. 1. Axial sections show significantly active regions during response inhibition in abstinent alcohol dependent subjects (upper row) and healthy controls (bottom row), resulting from single-sample t-tests (NoGo_alcohol + neutral > Go_alcohol + neutral) within each group. The significant statistic threshold for clusters is set at $p < 0.001$ (Family wise error, after small volume correction).

related (e.g. beer bottle) or neutral objects (e.g. bench). These stimuli were part of a picture set that was rated in a pre-study by inpatients with AUD and controls along four dimensions (alcohol-relatedness, craving, arousal and valence). The pictures were additionally controlled for physical parameters such as visual complexity, luminance, and color [43]. Participants were instructed to press a button as soon as a picture appeared on the screen (Go-trials) and to refrain from responding when a picture appeared twice in succession (NoGo-trials). Using repetition as a NoGo signal is beneficial in that not only the NoGo trial, but the previous Go trial already created an alcohol-related (or neutral) context. The task consisted of 960 Go-stimuli (480 neutral/480 alcohol-related) and 120 NoGo-stimuli (60 neutral/60 alcohol-related), thereby creating enhanced response prepotency. Sixty blank trials completed the task. Stimuli were presented in a pseudorandomized order and each stimulus was on screen for 900 ms with an inter-trial interval of 100 ms.

2.4. Procedure

After signing the informed consent, all participants were assessed for potential exclusion criteria for MRI-scanning. Patients completed OCDS and HAMD in the University Hospital for Psychiatry one to seven days prior to fMRI-measurement. Control participants completed OCDS, BSI and HAMD upon arrival at the scanning site. Before the fMRI investigation, all participants were asked to take a breath alcohol level test, in which an alcohol level of 0.0‰ was required (Lion Alcometer SD-400). Prior to performing the Go/NoGo task in the fMRI scanner, participants performed a training session on the computer to become familiar with the task. For task administration and behavioral response recording, E-Prime v1.1 software (PST, Sharpsburg, PA, USA) was used and stimuli were presented on visuaStim Digital Goggles in the fMRI-scanner. After 10 min of performance, the participants had a two-minute break to relax before the second half of the task was administered. Overall, the task lasted approximately 25 min.

2.5. Statistical analyses of behavioral and self-report data

To assess Go/NoGo-task performance, both reaction times and error rates were compared. Reaction times (RTs) in Go trials and RTs during errors of commission (EOC) in NoGo trials were analyzed using a repeated measures analysis of covariance (2×2 ANCOVA), imputing context (alcohol, neutral) as the within-subjects variable and group (patients, controls) as the between-subjects variable, while age and gender were used as covariates. Because percentage of errors on Go (errors of omission) and NoGo (EOC) trials were not normally distributed ($p < 0.05$ in Shapiro-Wilk test), Mann-Whitney U tests of independent samples were used to test the between-group comparisons, while within-group differences were analyzed with Wilcoxon signed-rank tests.

Group comparisons regarding age were conducted with a *t*-test, for gender with a Chi-square test and because of non-normal distribution (assessed with Kolmogorov-Smirnov test) with a Mann-Whitney-U-test for education, HAMD and OCDS. For all analyses, a significance level of $\alpha \leq 0.05$ was used.

2.6. fMRI data

2.6.1. Image acquisition and preprocessing

Imaging data were acquired on a 3 T Siemens Magnetom Trio TIM Scanner System (located at the Neuroradiology Department of the Inselspital, Bern) with a standard 12-channel radio frequency head coil. The structural images were collected using a three-dimension (3D) magnetization-prepared rapid gradient-echo (MP-RAGE) T1-weighted sequence (repetition time (TR) = 1950 ms, echo time (TE) = 2.2 ms, inversion time (Ti) = 900 ms, and a flip angle (FA) = 9° field of view (FOV) $256 \times 256 \text{ mm}^2$, matrix dimension 256×256 , resolution $1 \times 1 \times 1 \text{ mm}^3$). The functional session started with the Go/NoGo task. While

subjects were performing the task, functional imaging was acquired using a T2*-weighted Echo Planar Imaging (EPI) sequence (TR = 2000 ms, TE = 30 ms, FA = 90°, FOV $192 \times 192 \text{ mm}^2$, matrix dimension 64×64 , 32 axial slices positioned along the anterior and posterior commissures with a slice thickness of 3.0 mm, a gap of 0.75 mm, and a resolution of $3 \times 3 \times 3.75 \text{ mm}^3$).

Image pre-processing was conducted using SPM12 (Wellcome Trust Center for Neuroimaging, University College, London, UK) within MATLAB 9.2 (Mathworks, Sherborn, MA, USA). For each participant, functional images were realigned with a least square rigid body transformation, to minimize the effects of head movements. All functional images were then co-registered to the individual anatomical image and normalized to the standard Montreal Neurological Institute (MNI) space. Finally, images were smoothed with an isotropic Gaussian kernel of 8 mm full width at half maximum (FWHM) to increase signal-to-noise-ratio and to minimize residual differences in gyral anatomy.

2.6.2. Statistical analyses of fMRI data

First level analysis. Whole brain analyses of the functional images were also performed using SPM12. The pre-processed functional images were analyzed statistically using a generalized linear model (GLM) approach. For subject-level analysis, seven event types were specified: Go_alcohol_correct, Go_neutral_correct, NoGo_alcohol_correct, NoGo_neutral_correct, NoGo_alcohol_error, NoGo_neutral_error, and Blank. Event types were specified at the time of indicator onset and modeled as delta functions convolved with the canonical hemodynamic response function (HRF). Realignment parameters (6 parameters in total) were included as multiple regressors in the GLM model to correct for head movement. Following that, single-subject *t*-contrasts were conducted for correct trials: (NoGo_alcohol + neutral > Go_alcohol + neutral), (NoGo_alcohol > Go_alcohol), (NoGo_neutral > Go_neutral). Because this study focused on the neural responses during successful inhibition, statistical analyses included only correct Go and NoGo trials. This first-level analysis generated parameter estimates for each condition of interest in every subject.

Second level analysis. Second level random-effects analyses were then performed on individual contrast images. As a basic affirmation that our task broadly activated structures of the inhibition-related network within each group, one sample *t*-tests were separately conducted for each group (NoGo_alcohol + neutral > Go_alcohol + neutral). To explore all potential effects of context and group on neurophysiological correlates of inhibition, the context-specific first level contrasts (NoGo_alcohol > Go_alcohol and NoGo_neutral > Go_neutral) were entered into a 2×2 ANCOVA, with context (alcohol and neutral) as the within-subject variables and group (patients and controls) as the between-subject variables, while age and gender were used as covariates. As the main question of this study focused on the effect that an alcohol-related context has on inhibitory functioning in patients with AUD, planned single sample *t*-tests were conducted separately within each group for [(NoGo_alcohol > Go_alcohol) > (NoGo_neutral > Go_neutral)], and vice versa. A threshold of $p < 0.001$ was first applied to the whole-brain image. Clusters within the inhibitory control network (IFG, DLPFC, medial prefrontal cortex, ACC, (Pre-)SMA, premotor cortex, PCC, putamen, thalamus, and inferior parietal cortex) were deemed significant if $p < 0.05$ family-wise error (FWE) corrected, after small volume correction (8 mm, peak-level). The above mentioned regions of interest in the inhibitory network were defined based on meta-analyses and large-scale fMRI studies on inhibition [20,24], on studies investigating general inhibition in relation to addiction [28,29,44] and on prior own work investigating alcohol-specific inhibition in patients with AUD [34]. Clusters that were located outside this inhibitory control network and met the defined statistical threshold were marked and reported for completeness (however, as they were not part of the regional hypotheses, the application of a small volume correction might not be sufficient for these regions and such findings have to be interpreted with extra caution).

Correlation analysis. As stated above, we hypothesized that individual craving enhances conflict and thus impedes inhibition in an alcohol-related context in AUD patients, thereby demanding additional resources in the ACC or PCC regions. We thus extracted the beta values from the respective clusters obtained with the planned contrast which isolated alcohol-related inhibition [(NoGo_alcohol > Go_alcohol) > (NoGo_neutral > Go_neutral)]. We then investigated whether the observed activation differences in these clusters correlated with subjective craving as measured with the OCDS-C subscale. We used Pearson's correlations to investigate the relationship between subjective craving scores and brain activation related to alcohol-specific inhibition (i.e. beta-difference [(NoGo_alcohol > Go_alcohol) - (NoGo_neutral > Go_neutral)]) in these clusters. These analyses were carried out using the IBM SPSS Statistics software (version 25.0).

Visualization of all neuroimaging data were performed using xjview (extension toolbox (<http://www.alivelearn.net/xjview8>)) and self-written MATLAB scripts. For the labeling of the clusters, we checked the regions indicated in SPM and the Yale BioImage Suite for the peak coordinate. If the peak was undefined or if the two labels did not align, xjview was used to identify the region in which the majority of voxels was located.

3. Results

3.1. Descriptive and behavioral data

Table 1 summarizes age, education and other characteristics of the study participants. In the AUD group, all patients had a history of years of alcohol problems (ranging from 2 to > 20 years). At the time of fMRI measurement, patients were abstinent for 14–45 days (mean: 27.5; standard deviation: 9.8). Out of 13 AUD patients, 8 were currently on psychopharmaceutical drugs (see SOM 1 for more details). Regarding psychiatric comorbidities, 2 of the patients were also diagnosed with personality disorder, 3 with depressive disorders and 1 had a history of anxiety disorder (but note that in all cases, alcohol dependence was considered the primary diagnosis, see also 2.1). Despite our attempt to recruit a control group with comparable educational levels, controls had more years of education than patients (Table 1). As expected, compared to the control group, the AUD group had significantly higher OCDS scores, confirming participants' enhanced craving for alcohol. 5 of the 13 patients and 3 of the 14 controls were smokers. Concerning other substance use, one subject in the control group occasionally consumed cannabis. In the AUD group, two patients occasionally consumed cocaine and one of those two also had a history of harmful cannabis use (but was abstinent for the last 6 years). Age and gender did not differ significantly between groups, but were included as covariates in our analyses, as groups were not balanced.

Reaction times. Table 2 summarizes reaction times of both groups

Table 1
Demographics and psychological variables of the AUD and control groups.

	AUD Group	Control Group	statistic	p value
Total N	13	14		
gender (m/f)	10/3	9/5	$\chi^2 = 0.52$	0.472
	M (\pm SD)	M (\pm SD)		
Age (years)	45.62 (\pm 10.01)	37.71 (\pm 12.82)	$t = 1.79$	0.086
Education (years)	13.08 (\pm 1.75)	14.78 (\pm 2.22)	$U = 49.5$	0.043*
OCDS-O	14.92 (\pm 10.53)	3.07 (\pm 3.08)	$U = 33.5$	0.004*
OCDS-C	8.31 (\pm 6.17)	2.43 (\pm 1.87)	$U = 48.0$	0.038*
HAMD	5.77 (\pm 3.65)	1.07 (\pm 1.27)	$U = 18.5$	<0.001*

Abbreviations: M = Mean; SD = standard deviation; OCDS-O = Obsessive compulsive drinking scale - overall score; OCDS-C = Obsessive compulsive drinking scale - compulsion subscale; HAMD = Hamilton depression scale; m = male; f = female. *indicates $p < 0.05$. Note that significance was computed with a Chi-square test for gender, with a t -test for age and with a Mann-Whitney-U-test for Education, HAMD and OCDS.

Table 2
Reaction times (ms) of the AUD and control groups in Go and NoGo trials.

	AUD Group Mean \pm (SD)	Control Group Mean \pm (SD)
RT GO	447.96 (\pm 93.08)	403.23 (\pm 78.61)
RT GO - ALC	449.00 (\pm 92.07)	404.47 (\pm 80.38)
RT GO - NEU	446.92 (\pm 97.83)	402.00 (\pm 79.83)
RT NOGO (EOC)	363.92 (\pm 99.4)	336.24 (\pm 78.65)
RT NOGO - ALC	366.63 (\pm 109.03)	332.89 (\pm 332.89)
RT NOGO - NEU	361.21 (\pm 93.17)	339.59 (\pm 74.61)

Abbreviations: SD = standard deviation; RT = reaction time; ALC = Alcohol related stimuli; NEU = neutral stimuli; Error of Commission = Erroneous button press on NOGO trials. Note that neither the group differences, nor the difference between alcohol related and neutral stimuli, nor their interaction reached significance.

and contexts. No significant main effects or interactions for the factors groups or context were observed for reaction times during NoGo or Go trials (all $F_s < 0.25$, all p -values > 0.6, see also Table 1 in supplementary online material)

Error rates. No significant differences between groups were observed for error rates on NoGo trials (Errors of commission, EOCs) or Go trials (errors of omission, EOO). On a merely descriptive level, the overall percentage of EOCs (pooled over alcohol-related and neutral contexts) was slightly lower in the AUD group (Mean (M): 20.48, standard deviation (SD): \pm 14.65) than in the control group (M:24.67, SD: \pm 18.00), a pattern driven by lower EOCs in the alcohol-related context in patients with AUD (see also Table 3). However, within-group analyses revealed a significant difference between alcohol-related and neutral contexts in the group of AUD patients for error of commissions, but not in the control group (Table 3, upper rows). Considering the Go trials, within-group analyses revealed a significant difference in error rates between alcohol-related and neutral context in healthy controls, but not in the AUD group (Table 3, lower rows).

3.2. fMRI data

Inhibition-related network

To ensure that our task activated the inhibitory network and to explore the nature of the inhibition-related network within each group separately, single-sample t -tests were conducted within each group (NoGo_alcohol + neutral > Go_alcohol + neutral). As expected, successful response inhibition recruited for both groups (AUD and HC) a fronto-striatal-parietal network (Fig. 1).

ANCOVA

A 2×2 ANCOVA was conducted on the context-specific first level

Table 3
Groupwise comparison of Go/NoGo task performance.

	ALC Mean \pm (SD)	NEU Mean \pm (SD)	z	p
% Errors of Commission (on NoGo trials)				
AUD group	17.57 (\pm 13.24)	23.45 (\pm 16.40)	-2.94	0.003*
CON group	24.17 (\pm 18.49)	25.24 (\pm 18.71)	-0.11	0.916
% Errors of Omission (on Go trials)				
AUD group	2.63 (\pm 3.72)	2.11 (\pm 2.96)	-1.72	0.086
CON group	1.21 (\pm 1.59)	0.8 (\pm 1.25)	-2.36	0.018*

Abbreviations: AUD = Alcohol Use Disorder; CON = Control; ALC = Alcohol related stimuli; NEU = neutral stimuli; Error of Commission = Erroneous presses on NOGO trials; Error of Omission = Erroneous non-presses on Go trials; SD = standard deviation.

contrasts (NoGo_alcohol > Go_alcohol and NoGo_neutral > Go_neutral) to explore all the potential effects of group (patients, controls) and context (alcohol, neutral) as well as their interaction on neurophysiological correlates of inhibition, using age and gender as covariates. This analysis showed a main effect of group and condition, but no condition by group interaction. The AUD group displayed more BOLD activation than controls in all areas, where significant group differences were observed (hyper-activation). Differences were prominent in frontal (superior and medial frontal gyrus, precentral gyrus, ACC) and parietal (precuneus, postcentral gyrus) regions as well as in a midbrain-cluster spanning the thalamus and midbrain areas (see also Table 4). The main effect of condition revealed significantly more BOLD activation for the alcohol-related pictures compared to neutral pictures in bilateral occipital regions, the right (pre)cuneus, left medial frontal gyrus, and bilateral ACC (see Table 2 in the supplementary online material)

Planned contrast isolating alcohol-related inhibition

Because this study aimed to investigate the effect of an alcohol-related context on neuronal correlates of inhibitory functioning in patients with AUD, we conducted planned single sample *t*-tests within each group separately to investigate this alcohol-specific inhibition. This planned contrast, which isolated alcohol-related inhibition in the AUD group [(NoGo_alcohol > Go_alcohol) > (NoGo_neutral > Go_neutral)], revealed increased activation in fronto-striatal-parietal structures for the alcohol-related relative to the neutral context (Table 5). Particularly, increased activation for alcohol-specific inhibition was observed bilaterally in the anterior cingulate gyrus, left middle cingulate gyrus, right medial and prefrontal gyri, right putamen, left inferior parietal cortex, right precuneus, and right operculum. Table 5 provides MNI coordinates for the voxel of maximum intensity in each cluster. Beta values for these clusters are depicted in Fig. 2 in supplementary online material. No such effect was found in the HC group or in the reverse *t*-test examining higher activation in neutral as compared to alcohol-related inhibition in the group of patients.

Correlation analyses

Correlation analyses investigated a potential association between neuronal ACC activation during alcohol-related inhibition (assessed via

Table 4

ANCOVA, main effect of group: Brain regions with higher activation in AUD (vs. controls) during successful NoGo trials in both contexts (NoGo_alcohol > Go_alcohol and NoGo_neutral > Go_neutral). Note that this contrast yielded no regions with higher activation in controls (vs. AUD).

Activated areas	MNI peak coordinate	Cluster size	<i>F</i> (148)	<i>p</i> value
R Superior frontal gyrus (med)	8 58 18	5	14.01	0.040
R Superior frontal gyrus (med)	2 50 40	7	16.57	0.018
L Superior frontal gyrus	-20 -22 54	5	14.14	0.038
L Anterior cingulate cortex	-4 26 -4	10	16.65	0.006
Thalamus/midbrain	2 -12 -6	23	21.82	0.003
L Hippocampus*	-38 -24 -8	9	19.53	0.007
L Postcentral gyrus*	-46 -20 62	9	18.92	0.008
L Precuneus*	-22 -72 18	9	16.79	0.016
L Middle temporal gyrus*	-56 -20 -18	12	18.83	0.009
L Superior temporal gyrus*	-36 -40 6	6	16.84	0.016
R fusiform gyrus*	44 -62 -14	7	13.89	0.041
R Cuneus/Calcarine cortex*	12 -78 12	101	18.95	0.008
L Lingual gyrus*	-22 -58 0	10	14.80	0.031
L Cuneus/posterior Cingulate*	-4 -70 12	15	16.52	0.018

Cluster-level significance: $p < 0.05$ (FWE corrected (peak-level), after small-volume correction); Regions were labelled using *xjview* software and the Yale BioImage Suite package; Abbreviations: MNI = Montreal Neurological Institute; L = left; R = right; *These regions are reported for the sake of completeness. Note however, that they are not located in the inhibitory control network as defined in our hypotheses, for which our analyses were designed.

Table 5

Planned contrast: Whole brain functional MRI results comparing BOLD response during successful NoGo trials (alcohol vs. neutral) of the AUD group.

Activated areas	MNI peak Coordinate	Cluster size	<i>t</i>	<i>p</i> value
L Superior frontal gyrus (med.)	-12 46 30	16	4.19	0.006
R Superior frontal gyrus (med.)	18 50 12	6	3.69	0.023
R Precentral gyrus	52 -6 32	16	3.74	0.020
L Anterior cingulate cortex/medial frontal cortex	-18 44 -2	31	4.52	0.003
R Anterior cingulate cortex	6 26 12	25	5.14	<0.001
L Anterior cingulate cortex	-6 30 2	33	4.38	0.004
R Putamen	26 -6 8	9	3.79	0.018
L inferior parietal cortex/superior temporal gyrus	-46 -32 14	7	3.68	0.023
L Middle cingulate gyrus*	-12 8 32	17	4.04	0.010
R Rolandic operculum*	52 2 6	9	4.10	0.008
R Precuneus*	20 -52 34	25	4.44	0.003

All listed clusters reach cluster-level significance ($p < 0.05$, FWE corrected, after small-volume correction); Labeling of the regions was conducted according to SPM, the Yale BioImage Suite and the *xjview* package. Abbreviations: L = left, R = right, med = medial; *These regions are reported for the sake of completeness. Note however, that they are not located in the inhibitory control network as defined in our hypotheses, for which our analyses were designed.

individual beta value differences extracted from the three ACC clusters obtained with the planned contrast that isolated alcohol-related inhibition) and subjectively experienced craving (i.e. compulsive drinking urges). Because no such cluster was observed in the control group, this analysis was restricted to the 13 patients with AUD. As the planned contrast yielded no PCC cluster, this association could not be tested for the PCC as planned. The analysis revealed significant correlations between subjective craving scores and BOLD response in one cluster in the right ACC ($r = 0.67$, $p = 0.0078$, Fig. 2). No other clusters showed a significant relationship between craving score and BOLD response.

4. Discussion

The present study investigated neurophysiological correlates of alcohol-related inhibition in patients with AUD by measuring BOLD fMRI during performance of a newly developed Go/NoGo-task with alcohol-related and neutral stimuli.

4.1. Comparison of inhibitory activity between patients and controls

Preliminary results indicate that successful response inhibition recruited a fronto-striatal-parietal network for both groups (AUD and controls), which largely confirmed previous findings [11,17,20,24]. When comparing neuronal activation during successful inhibition between groups, AUD patients showed enhanced activation in regions including the ACC, medial & lateral superior frontal gyri (SFG), and the thalamus. These findings are consistent with earlier studies reporting inhibition-related hyperactivation in ACC [18,29,33], thalamus [27] and medial SFG [32] in SUD patients during inhibition. However, we did not replicate the finding of enhanced inhibitory activation in lateral DLPFC in SUD patients [28,31,32]. Other than variations in SUD groups (alcohol, cocaine, or cannabis users) and task details [45], this discrepancy might also be due to differences in analytic strategy and contrasts used. While the present analysis worked with NoGo minus Go contrasts (created on the first level analysis and entered in subsequent analyses) to focus on inhibition, the three studies mentioned above [28, 31,32] contrasted NoGo trials to a tonic task-related baseline. It is thus possible that such a contrast yields a more extensive neuronal substrate including regions involved not only in inhibition but also in response selection [20].

As all regions with differential activation between groups showed higher activation in AUD patients, the present study adds to the existing

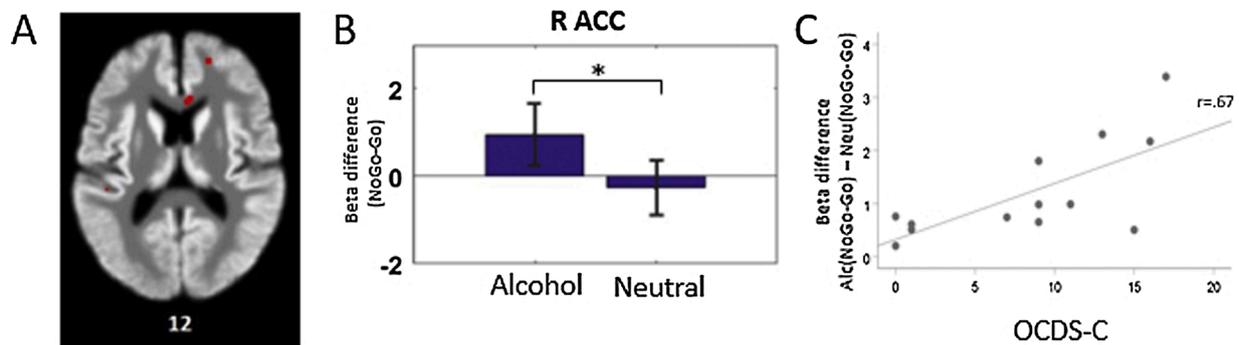


Fig. 2. **A:** cluster in right anterior cingulate cortex (ACC, shown at MNI coordinate $z = 12$) in which AUD patients showed higher activation during alcohol-specific inhibition ([NoGo_{alc} > Go_{alc}] > [NoGo_{neutral} > Go_{neutral}]). **B:** Significant beta differences (NoGo-trials minus Go-trials) extracted from the right ACC-cluster for alcohol-related as well as for neutral inhibition. **C:** Positive associations between subjective craving (indicated by OCDS-C score) and enhanced activation during alcohol-related vs. neutral inhibition (indicated by beta differences) in the group of 13 AUD patients.

evidence for hyperactivation in the inhibitory network in SUD. Our findings are thus in line with other studies reporting hyperactivation during inhibitory tasks in SUD when patients and controls performed comparably (e.g. [9,28,29,31–33]). Interestingly, most studies describing an opposite pattern (hypoactivation) also reported differences in task performance between patients and controls (e.g. [19,25,26]);). This pattern is in line with the interpretation that hyperactivation in inhibition-related structures (in absence of performance deficits) is a necessary form of functional compensation to inhibit responses successfully [32,33,46,47]. However, whether sample characteristics (e.g. severity or chronicity of substance use problems), difference in task design or other factors determine if similar task performance is achieved – maybe through neuronal compensation – still remains unclear. In the light of our finding of activation differences in ACC, thalamus as well as medial and lateral SFG and in the context of a possible interpretation of this activation as a form of functional compensation, it is noteworthy that these regions have been reported to mediate the association between AUDIT scores and reduced inhibitory capacity (albeit in a non-problematic, young, social drinking sample, Hu, Zhang, Chao, Krystal, & Li, 2016).

4.2. Alcohol-specific inhibition in AUD patients

In the planned contrast carried out to isolate neuronal correlates of alcohol-specific inhibition in the group of AUD patients, we observed several regions with significantly enhanced activation during alcohol-related (vs. neutral) inhibition. No clusters with higher activation during neutral inhibition were observed, neither yielded the same analysis in the healthy control group any clusters with higher activation during alcohol-related (vs. neutral) inhibition. This suggests that alcohol-related inhibition selectively demands more resources in patients with AUD. Regions activated more strongly during alcohol-related inhibition included the bilateral ACC, right medial and prefrontal gyrus, right putamen, and left inferior parietal cortex, which are located in the inhibition network. In the right ACC, the extent to which activation increased from neutral to alcohol-related inhibition was furthermore correlated with the subjective amount of alcohol-related craving. The ACC has been related to difficult executive tasks [48,49], particularly to performance monitoring processes, including detection of cognitive conflict [36], and emotional response inhibition [50]. The here reported enhanced activation in the ACC during alcohol-related as opposed to neutral inhibition in patients with AUD, as well as the observed association between this increase and craving, is in line with the ACC's role in conflict monitoring, which might be enhanced during alcohol-related inhibition in AUD patients, particularly when craving is high. Such an interpretation corresponds to neuroscientific models [6], which postulate a competition between enhanced cue-reactivity and diminished inhibitory control resources.

Interestingly, an earlier analysis of event-related potentials (ERP) from the present study [34] showed that the N2-component, which is thought to reflect conflict, is altered in alcohol-related inhibition in AUD patients and that this alteration varies with the subjective amount of craving. However, source analysis localized this N2 effect to the PCC but not the ACC. A potential association between PCC activation and craving was not tested in the present fMRI-study because the planned contrast, contrary to our hypotheses, did not yield a PCC cluster. This variation in localization might reflect the fact that EEG and fMRI are sensitive to different parts of neuronal activation. EEG is sensitive to simultaneous activation of similarly oriented neurons on a time scale with very high resolution while fMRI is dependent on neuronal activation producing differences in blood oxygenation, working with high spatial resolution on a broader time scale. Alternatively, the discrepancy might be due to the ERP analysis being conducted with the NoGo-ERPs and not with the difference waves (NoGo minus Go), which would have been the more precise equivalent to the present fMRI analysis.

The medial SFG and the putamen were also observed to display higher activation during alcohol-related compared to neutral inhibition in the AUD group. Anatomically connected to the anterior and mid-cingulate gyri [51], the medial SFG has been related to performance monitoring and cognitive control [52] and has previously been reported in similar studies of AUD and SUD patients [32,33]. The putamen, which is part of the network subserving drives and motivation, is highly relevant to AUD [6], and has been thought to modulate the balance between goal-directed actions and habitual behaviors [53]. Higher activation in the putamen during alcohol-related as opposed to neutral NoGo-trials in the AUD group might indicate that the adjustment between the prepotent action tendency to respond and the task demand to withhold that response is harder during alcohol-related NoGo trials, maybe due to well-established drinking habits.

When comparing our findings to two earlier studies using alcohol-related stimuli in a Go/NoGo task [18,33], one has to keep in mind that our analyses worked with context-specific contrast images (NoGo_{alcohol} minus Go_{alcohol}; NoGo_{neutral} minus Go_{neutral}) in order to focus on alcohol-related inhibition and to disentangle effects of stimulus type (alcohol-related, neutral) and trial type (Go, NoGo). On the contrary, Czapla et al. [33] contrasted alcohol-related NoGo trials to neutral Go trials and compared this to a contrast of neutral NoGo and neutral Go trials. Here, they observed higher activation in occipital areas in AUD patients compared to controls and interpreted this by stating that the higher salience and complexity of the alcohol-related stimuli makes inhibition require more effort. In line with the salience-part of this interpretation, we also observed a stimulus type-effect in occipital regions (see ANCOVA results and Table 2 in SOM), albeit in both groups. The planned contrast which isolated alcohol-related inhibition (as opposed to neutral inhibition) in AUD patients did not, however, yield any clusters in occipital areas. Ames et al. [18] compared alcohol-related

NoGo trials directly to neutral Go trials and observed higher activation in the DLPFC, ACC, and right anterior insula in heavy compared to light drinkers. Overlapping with these findings, we observed higher ACC activation during alcohol-related inhibition in AUD patients, suggesting that enhanced demands are placed on this region during alcohol-related inhibition. While we did observe DLPFC activation for general inhibition, this region was not selectively more activated in an alcohol-related context in AUD patients, suggesting that the DLPFC finding in Ames et al. might rather be attributable to inhibition in general than to inhibition in an alcohol-related context.

Taken together, the present findings indicate that the task presented here allows to investigate alcohol-specific inhibition in a sample of patients with AUD. Our preliminary results suggest that inhibition in an alcohol-related context demands additional resources in patients with AUD and enhances conflict between the tendency to respond and the task demand to inhibit this response.

4.3. Limitations

The findings of the present study should be viewed with some limitations. First and foremost, the sample of the present study lends a preliminary character to our results, as their replicability and generalizability is strongly limited by the small size and considerably heterogeneity of our sample [54]. Thus, while our data suggest that the task presented here is suited to investigate alcohol-specific inhibition in patients with AUD, the observed significant differences await replication with larger sample sizes. Additionally, important parameters describing the patient group were not available, such as details of the duration and severity of drinking problems, which could further contribute to elucidating the harmful effects of problematic alcohol use on neurofunctional mechanisms. Also, the patient and control group differed in education levels, we thus cannot rule out that differences in the general level of cognitive functioning, which might also have existed prior to AUD onset, influenced our results. While such an interpretation is plausible regarding the main effect of group, which indicated a hyperactivation in the inhibitory network in patients with AUD, it is less conceivable for the differential hyperactivation in alcohol-related inhibition in the patient sample.

Also, with respect to the Go-NoGo-task used to measure inhibitory control, two aspects need to be considered: First, performance of the Go-NoGo-task can be biased by attentional influences [21]. Thus, the stop signal reaction time (SSRT) derived from a stop signal task, which allows to assess response inhibition relatively independent of attention [21,55] might offer an interesting alternative. While this is true for the assessment of general response inhibition, where stop signal tasks have provided an excellent opportunity for research both in healthy samples [55, 56] and subjects with substance use disorders [21], a stop signal task incorporating alcohol-specific as well as neutral inhibition has yet to be developed. Second, inhibitory control also involves a proactive component [57], possibly altered in patients with AUD [58], which might be affected by the presentation of alcohol-related cues. Behaviorally, in a Go-NoGo-task, proactive control is typically linked to reaction times on Go-trials. While patients with AUD were (on a descriptive level) slightly slower than controls on both alcohol-related and neutral Go trials (Table 2), we observed no significant effects of group, context or their interaction. At least for the results concerning alcohol-specific results, it thus seems unlikely that they are due to differences in proactive control. Regarding the differences in general inhibition, such an effect still seems possible due to the general (albeit insignificant) slowing in the patients group. Finally, we did not tailor the stimuli according to our patients drinking preferences, which would have been a good way to enhance individually attributed salience [33].

4.4. Conclusion

To the best of our knowledge, this is the first study to investigate

alcohol-related inhibition in AUD using a Go/NoGo task with neutral and alcohol-related Go and NoGo stimuli while fMRI was recorded. In conclusion, our preliminary results indicate that abstinent AUD patients exhibit an increased BOLD response in the inhibitory network during successful response inhibition. An alcohol-related context further increases this activation in important parts of this network, including the ACC, medial SFG, and putamen. In the ACC, this activation increase during alcohol-related inhibition is furthermore related to subjective craving. This study thus presents a new task to study inhibition in an alcohol-related context and expands our knowledge on the neuronal basis of alcohol-related inhibition. It indicates that the presence of alcohol-related stimuli enhances conflict, especially in patients experiencing strong craving, and thus places additional demands on an already challenged inhibitory system. Thus, developing interventions that address inhibitory challenges in alcohol-related contexts specifically in this subgroup of patients might thus be a valuable contribution to relapse prevention treatment programs.

Author statement

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.bbr.2020.112973>.

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