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Using Imagination to Integrate Contextual Effects in a Cue-Reactivity Paradigm in Patients with Alcohol Use Disorder: A Functional Magnetic Resonance Imaging Pilot Study

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Keywords
Alcohol use disorder · Context · Imagination task · Cue reactivity · Functional magnetic resonance imaging

Abstract
Introduction: In individuals with alcohol use disorder (AUD), the brain areas underlying cue-induced reactions (e.g., cingulum, striatum, thalamus) and altered activation of these regions have been identified by functional neuroimaging. Neuronal responses to a complex alcohol-related context are yet to investigate. To better understand contextual effects as well as the interplay of cue-induced neural reactions and context exposure, the present study implemented an imagination procedure during functional magnetic resonance imaging (fMRI). ***Methods:*** Thirteen patients with AUD and 13 healthy controls completed two rounds of a cue-reactivity paradigm inside an MRI scanner. Two individualized imagination tasks were conducted before each of the two cue reactivity tasks. A 2 (group) × 2 (imagination) × 2 (picture-type) analysis of variance (ANOVA) was performed. ***Results:*** The ANOVA revealed a main effect for imagination with higher activation in bilateral thalamus and right caudate nucleus and an interaction effect between imagination and group in right thalamus and left caudate nucleus, due to the patient group reacting stronger during alcohol-related imagination. These structures are involved in relaying sensory information and habit learning. No main or interaction effects of picture type were observed. ***Conclusions:*** These results support the view that context effects alter the neural responses in thalamus and nucleus caudatus in patients with AUD, and that imagination tasks are suited to incorporate contextual influences in neurophysiological research designs. Future research needs to investigate whether the failure to observe a picture-type effect was due to limited statistical power and omission to individualize picture set, or whether an imagination procedure interferes with the evocation of picture-type effects.

Introduction

High relapse rates after treatment for alcohol use disorders (AUD) remain a major concern. Despite the beneficial effects of relapse prevention treatment, abstinence rates decrease substantially within the first month after discharge [1, 2].

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One factor that enhances the relapse risk is exposure to stimuli (cues) that are regularly associated with alcohol intake [3–5]. Such stimuli can become conditioned cues that elicit alcohol craving and subsequent drinking as conditioned responses [6, 7]. However, these stimuli are usually encountered in a broader context, which becomes habitually related to alcohol intake. Such contexts comprise environmental factors, such as a bar [8] or a particular social situation [9], as well as internal triggers, such as feelings [10] and cognitions [11]. In animals, returning to a multimodal context habitually related to alcohol intake provokes reinstatement of drug use [12, 13]. In humans, contextual factors, such as certain situations, times of day, or emotional states, have been shown to increase craving [14]. For patients with AUD, even if the urge to consume declines considerably during treatment, confrontation with a situation in which consumption usually occurred before treatment still poses a high risk for relapse, [15]. Like specific cues, these contextual factors can activate goals, cognitions, and behaviours in an implicit and automatized manner [16, 17]. Therefore, the influence of contextual factors should be considered in the investigation of potential precursors of alcohol consumption and relapse [18].

Research investigating contextual influences on AUD has primarily focused on cue reactivity, which comprises automatic and subconscious reactions to specific alcohol-related stimuli, such as the sight, taste, or smell of an alcoholic beverage [19, 20]. The evidence supporting cue reactivity is multifaceted, and based on different types of assessments such as self-reports, as well as behavioural and neurophysiological measures. On a neurophysiological level, a meta-analysis [21] has summarized the neural basis for cue-induced reactions [5, 22–24]. The areas identified include structures related to the brain's reward prediction system and habit learning (striatum, including caudate nucleus and putamen), interoception and emotion processing (insula), the relay of sensory information (thalamus), attention, motivation, and cognition (cingulate cortex), decision-making (medial prefrontal cortex), mental imagery and episodic memory (precuneus), and consciousness (claustrum). Furthermore, in subjects with AUD (compared to healthy controls), the presentation of positive versus neutral stimuli increased activation of the posterior cingulate, precuneus, superior temporal gyrus, ventral striatum, and thalamus [25]. When exposure to alcohol cues was combined with a sip from an alcoholic beverage, subjects with AUD (but not the controls) showed increased brain activities in the left dorsolateral prefrontal cortex and the thalamus [26]. Additionally, cue-elicited brain activity in the medial prefrontal cortex, the thalamus, and the ventral and dorsal striatum has been shown to differentiate between successful abstainers and relapsing patients with alcohol [27, 28] or nicotine [29] addiction. Thus, activation changes in these areas may be predictive of relapse [22].

Human research studies on neurophysiological cue reactivity have mainly used isolated stimuli as cues. While these studies provided a better understanding of factors triggering relapse detached from social environment or contextual influences [30], the lack of contextual variety and complex, multimodal influences limits the ecological validity. The combined experience of discrete and contextual alcohol cues may be a more potent trigger for relapse than either type of cue alone [31, 32] and cue-induced alcohol craving measured in laboratory settings is likely to underestimate the craving severity that would be observed in contexts associated with alcohol consumption [33]. A typical context for drug use comprises situational factors, such as time, place, people, and internal states including cognitions and emotions. Context is broadly defined as a configuration of multimodal stimuli that comprise the backdrop within which alcohol intake occurs [4]. If all these factors act together and in combination with specific stimuli, the responses may be enhanced. Such considerations lead to calls that treatment methods as well as research designs must take the complex interplay between contextual factors and specific alcohol-related cues into account [12, 34].

Therefore, researchers have begun to incorporate context into experimental designs in order to assess reactivity evoked by alcohol-related cues under more ecologically valid experimental conditions [34, 35]. Nees et al. [36] indicated that contexts associated with alcohol consumption could influence cue reactivity in abstinent patients with AUD.

Newer technologies such as virtual reality (VR) offer the possibility to successfully simulate multisensory information from the real world and deliver it to a person through artificial means to make them feel as if they are in a virtual or imagined environment [37]. VR has the potential to exceed limits of traditional cue-reactivity paradigm by providing a virtual immersion in environments closely related to typical drug administration scenarios, thus achieving high levels of ecological validity [38, 39]. However, besides that fact that individualization of VR scenarios is difficult, VR is limited by its high costs and technical requirements during functional magnetic

resonance imaging (fMRI). Thus, VR remains underutilized in alcohol studies despite positive results [40]. Imagination techniques provide an easier way to simulate a personalized context in a cost-effective manner. Next to the ease with which scenarios can be tailored to reflect individually relevant alcohol-related situations, the advance of these techniques is their high scanner compatibility.

In the present fMRI study, we propose a way to incorporate context factors in a cue-reactivity paradigm in research on patients with AUD. An imagination task was implemented in the protocol to simulate contextual influences and to put participants in a naturalistic situation mentally. Imagination techniques enable an individual to see, hear, feel, or mentally interact with other individuals, objects, events, or situations [41]. These techniques have been evaluated for cognitive behavioural therapies. Meichenbaum [42] based the efficacy of imaginative methods on changing the inner dialogues and learning alternatives. In patients with AUD, imaginative techniques provide the opportunity to explore difficult situations and find constructive solutions [41]. A food-craving study [43] demonstrated the feasibility of imagination inside an MRI scanner and showed that imagination techniques can activate neuronal circuits similar to realistic stimulations. Furthermore, a non-clinical study in social drinkers [44] indicated that alcohol-related imagination increased activities in the cortico-limbic-striatal circuit.

Until now, most neurophysiological research on cue reactivity in patients with AUD has examined isolated stimuli in a laboratory context. To our knowledge, the effects of imagination-simulated context during an fMRI and the interactions with cue-induced responses have not yet been investigated in inpatients with AUD. Therefore, the present fMRI study aimed to (a) investigate the feasibility of an individualized, effective imagination of a drinking situation, and (b) provide an understanding of the neurophysiological underpinnings of contextual effects and their interactions with cue reactivity. More specifically, the present study used imagination techniques to mentally guide participants either to a context habitually related to alcohol use (e.g., a "typical" drinking context) or to a neutral context (e.g., an "every-day" context). In both contexts, a cue-reactivity paradigm was administered, while an fMRI sequence was running. In this way, the neurophysiology of contextual effects and their interactions with cue reactivity can be investigated.

Materials and Methods

Participants

The study protocol was approved by the Ethics Committee of the Canton Bern, Bern, Switzerland (KEK # 12/06). All participants provided written informed consent prior to inclusion. Of those included in the study, 13 were inpatients with AUD (10 male, 3 female; mean age: 45.46 years, range: 27–63 years) recruited during AUD treatment at the University Hospital of Psychiatry in Bern, Switzerland. All 13 patients met the diagnostic criteria for alcohol dependence syndrome as their primary diagnosis according to the International Classification of Disease, 10th edition, and reported a history of AUD for multiple years (range: 2–30 years). Patients were detoxified and finished withdrawal as part of their inpatient treatment. Patients were abstinent for a minimum period of 8 days (M = 28.15, SD = 13.47). Patients were excluded from participation if they experienced a moderate to a very severe depressive episode, which was assessed using the Hamilton Depression Rating Scale (HAMD [45]) or primary psychiatric illnesses (e.g., anxiety/personality disorder) or multiple use disorders (except nicotine), during recruitment. The following numbers of secondary diagnoses were present in our sample (multiple diagnoses are possible): one bipolar affective disorder, five mild depressive episodes, two emotionally unstable personality disorder, and one panic disorder. Thirteen healthy controls (nine males, four females; mean age: 42.23 years, range: 27–62) were recruited via an advertisement. A test battery comprising symptoms of AUD, psychopathology, cravings, and neurological illnesses was used to exclude unsuitable participants from the healthy control group, if symptoms were identified. Furthermore, 10 participants (6 patients, 4 controls) were habitual nicotine smokers.

Questionnaires, Material, and Tasks

Questionnaires

AUDIT. The Alcohol Use Disorder Identification Test (AUDIT [46]) is a short screening tool used to identify harmful drinking habits. An AUDIT score higher than 8 indicates a potential alcohol problem [47]. Healthy controls with scores higher than 8 were excluded from the study.

HAMD. The 21-item version of the Hamilton Depression Rating Scale (HAMD [45]) was used to screen all participants for existing depressive symptoms. Scores of 14 and higher indicate the presence of a moderate to a very severe depressive episode. Participants exceeding a cut-off score of 13 were excluded from the study.

BSI. The Brief Symptom Inventory (German Version [48]) was used to check for the presence of psychopathological symptoms in the control group. A global distress score (Global Severity Index [GSI]) was derived by calculating the mean of all scales. Results of the GSI are given in T values, where scores of 63 and higher are considered to reflect clinically relevant deviations [48]. Control subjects exceeding this cut-off value were excluded from the study.

OCDS. The Obsessive Compulsive Drinking Scale (OCDS-G; German Version [49]) is a 14-item screening tool used to assess cognitive and behavioural components of craving. The OCDS-G yields two subscale scores (for thoughts and compulsions) and an overall score, which is calculated by adding all item scores. Total scores can range from 0 to 56 (with higher scores indicating more severe intrusions and compulsions). In this study, the OCDS-G was not used as an inclusion criterion, but merely as a descriptive tool for both participant groups.

Materials

Stimulus Material

The stimulus material used in this study was obtained from a large database of standardized pictures, which contained 444 alcohol-related photographs, 387 neutral images, and 444 scrambled pictures [50]. All neutral and alcohol-related images were controlled for differences in complexity, luminance, and colour intensity. Scrambled pictures were created by first dissecting all alcohol-related images into pieces and then shuffling and reassembling these pieces. In addition to these adjustments, all alcohol-related and neutral pictures were rated according to their valence (i.e., the degree of positive or negative emotions evoked by the image) and alcohol-relatedness, as well as to the amount of arousal and craving evoked by viewing the image (i.e., whether the picture evoked strong or weak emotions and how strongly the image influenced the desire/urge to drink alcohol).

Task

Cue-Reactivity Task

In our study, we presented alcohol-related and neutral pictures to activate addiction-related processes and to provoke different responses (e.g., arousal, craving), similar to various brain imaging studies [51, 52]. The stimulus material described above was used to create eight different image sets, each consisting of 28 neutral, 28 alcohol-related, and 28 scrambled pictures. Every set was then extended by 28 blanks (or "non-events") and 9 question marks, which were interspersed throughout the set to conduct occasional vigilance checks. During the cue task, pictures were presented in a pseudo-randomized manner, with a presentation time of 2,000 ms and an inter-stimulus interval (ISI) of 1,900–2,100 ms. During this interval, a fixation cross was jittered on the screen. Before starting the task, participants received instructions to press a button every time a picture appeared, and to press a second button as fast as possible when a question mark was displayed. Overall, every participant completed two rounds of the cue-reactivity paradigm. To avoid repetition effects, participants received two different image sets, and the pictures were not repeated within the sets. To introduce the second independent measure (context), each of the two rounds was preceded by an additional task described in the following section.

Imagination Task

To systematically investigate the effects of context and their interactions with cue-induced activations, an imagination task (i.e., putting oneself mentally into a real-life situation [41]) was introduced in the study. During the imagination process, participants were guided to vividly picture themselves in either alcohol-related or neutral situations. For both imagination tasks, individualized scripts were developed and trained on a separate appointment prior to the fMRI session. Individualized scripts were tailored to incorporate as many sensory details and subjectively important thoughts as possible. To this aim, participants first reported the scenes as vividly as possible, meaning that they focused on specific sensory details, such as images, smells, and sounds, as well as emotions, thoughts, and motivational aspects associated with the perceptions. From these reports, the most salient aspects were incorporated into the imagination script. Imagination scripts for two types of situations were defined (1) a typical drinking situation (i.e., a scenario where they would usually consume and/or feelings of craving would usually emerge and remain high); and (2) a neutral everyday experience (i.e., a daily encountered scenario unrelated to alcohol consumption or feelings of craving). Once the scripts were finalized, the imagination procedure was performed under the guidance of a trained research assistant. The research assistant guided the participants to mentally experience the two types of scenarios. These training sessions were conducted prior to the fMRI appointment.

On the day of the fMRI appointment, every participant completed both a neutral and an alcohol-related imagination procedure, each of which was immediately followed by a cue-reactivity paradigm. A trained research assistant guided the participants through the imagination procedures inside the scanner. Participants were again instructed to imagine the scenarios as vividly as possible. The vividness of the imagination was recorded using a numerical rating scale (NRS, with scores ranging from 0 to 10) directly after the imagination task. Participants were then instructed to retain and to uphold the imagination (i.e., to mentally stay in that situation) during the subsequent cue-reactivity task. Vividness of the imagination was recorded on the NRS a second time at the end of the cue-reactivity task.

Scanning Procedure

All scanning took place at the University Hospital of Bern. Participants were greeted, then filled in an MRI questionnaire, and completed a breath test to assure an alcohol level of 0.00‰ during the test (Lion Alcolmeter SD-400; Lion Laboratories Limited, Barry, UK). Participants in the control group arrived approximately 1 h earlier to finish all assessment measures, whereas the inpatient group completed the HAMD and OCDS-G at the inpatient facilities before arrival. All tasks were explained before the participants entered the MRI scanner. A test run of the cue-reactivity paradigm using an independent set of 10 alcohol-related, 10 neutral, and 10 scrambled stimuli was completed on a computer. Inside the scanner, participants engaged in two rounds of the cue-reactivity paradigm, during which fMRI data were collected. Both rounds of the cue-reactivity paradigm were preceded by one of the two versions of the imagination tasks (alcohol-related or neutral). A research assistant guided the participants through the imagination procedures, during which no fMRI data were collected. Participants were instructed by the research assistant to imagine the scenarios as vividly as possible and to rate the vividness of the imagination on the NRS immediately after the imagination task (T1) and a second time immediately after the cue reactivity task (T2). To avoid sequence effects, the order in which participants engaged in the alcohol-related or neutral imagination procedure was randomized. Approximately half of all participants completed the neutral imagination during the first round and the alcohol-related imagination during the second round, while the other half experienced the reverse order. A 7-min break was incorporated between both sessions, during which anatomical images were acquired for coregistration purposes. The timeline of the procedure during fMRI is shown in Figure 1. The cue-reactivity paradigm was implemented in E-Prime 2.0 (Psychology Software Tools), and pictures were presented via VisuaStimDigital Goggles during functional image acquisition.

Statistical Analyses of Participant Characteristics, Vividness Ratings, and Behavioural Data

Age, gender, and smoking status (nicotine) were compared between the two participant groups using the Mann-Whitney test and likelihood ratio statistic for small and independent samples.

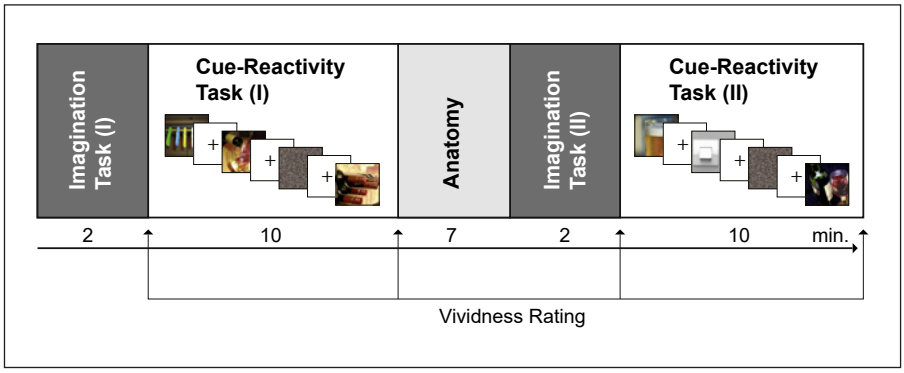


Fig. 1. Schema of all cognitive tasks and their respective durations during an fMRI and the time of vividness rating. The order in which the imagination tasks (alcohol-related vs. neutral) were completed was alternated between participants.

The scores of the questionnaires (HAMD and OCDS-G) between the two groups were compared with Levene's test for independent samples, equally for the difference in education (measured in years). Vividness scores of the two imagination tasks were compared between inpatients and controls using the Mann-Whitney non-parametric test. Demographics and vividness ratings were compared using SPSS for windows (IBM, version 27.0). Reaction times to the questions marks in the cue-reactivity task were analysed with a repeated measures ANOVA with the between-factor group (patients, controls) and the within-factor imagination task (alcohol-related, neutral). Errors (i.e., missing answers to the question marks) were analysed with a Mann-Whitney test.

MRI Data

Image Acquisition and Preprocessing

Neuroimaging was conducted at the Neuroradiology Department of the University Hospital in Bern using a 3T Siemens Magnetom TrioTim Scanner System (Siemens, Erlangen, Germany), which was provided with a standard 12-channel radiofrequency head coil. A 3D T1-weighted magnetization-prepared rapid gradient echo image was recorded for anatomical reference and to scan for neurological abnormalities (repetition time = 1,950 ms, echo time = 2.2 ms, inversion time = 900 ms, flip angle (α) = 9°, field of view = 256 × 256 mm, matrix dimension 256 × 256 mm, 1 × 1 × 1 mm^3 voxels). For fMRI, T2*-weighted images were acquired, while participants performed two sets of the cue paradigm using an echo planar imaging (EPI) sequence (repetition time = 2,000 ms, echo time = 30 ms, α = 90°, field of view 192 × 192 mm^2, matrix dimension 64 × 64 mm). Thirty-two axial slices positioned along the anterior commissure and the posterior commissure were taken (slice thickness = 3.0 mm, gap 0 mm), leading to an iso-voxel resolution of 3.0 × 3.0 × 3.0 mm^3. In total, 243 volumes were acquired within a total acquisition time of 8 min 12 s.

Analyses of all imaging data were analysed using SPM 12 (Wellcome Trust Centre for NeuroImaging, University College London, UK). Owing to the potential contribution of artefacts during the acquisition of the MR images, all fMRI data were pre-processed using a standard pipeline, as described below. First, all functional images were motion-corrected throughout the separate time series by realigning them to the first EPI image. This was done by performing a rigid-body spatial transformation using a least-square approach (i.e., Levenberg-Marquardt algorithm) and taking into account all six movement parameters (three translational: *x*, *y*, and *z*, and three rotational: α, β, and, γ). After adjustments, the average movements of all participants remained below 1 mm in all directions and did not differ between patients and controls (patients $x = -0.001$ mm, controls $x = 0.013$ mm, $t(50) = -1.68$, $p = 0.10$; patients $y = 0.029$ mm, controls $y = 0.0152$ mm, $t(50) = 1.14$, $p = 0.26$; patients $z = 0.036$ mm, controls $z = 0.0405$ mm, $t(50) = -0.30$, $p = 0.77$; patients $\alpha = 0.001°$, controls $\alpha = 0.001°$, $t(50) = -0.25$, $p = 0.80$; patients $\beta = 0.000°$, controls $\beta = 0.000°$, $t(50) = 1.02$, $p = 0.31$; patients $\gamma = 0.000°$, controls $\gamma = 0.000°$, $t(50) = -0.53$, $p = 0.60$). Next, the functional and anatomical images were co-registered using affine linear transformations. During this step, the 2D EPI images were resampled to fit the 3D T1 magnetization-prepared rapid gradient echo volume, meaning that the voxel dimensions of the 2D EPI images were resized to the iso-voxel 1 mm^3 dimension of the anatomical volume. All functional images were normalized by transforming them into the Montreal Neurological Institute standard space. This was accomplished by resampling all EPI images to the standard Montreal Neurological Institute dimensions (i.e., 91 × 109 × 91 with 2 mm^3-sized isotropic voxels). An isotropic Gaussian kernel with an 8 mm^3 full width at half maximum was then applied to all functional images for spatial smoothing.

Statistical Analyses of fMRI Data

Subject Level Analysis

Whole-brain statistical analyses were performed on all EPI images using a generalized linear model (GLM) approach. First, boxcar functions of all specified event types (alcohol-related, neutral, blanks, and scrambled images) were convoluted with the haemodynamic response function to model all predictors. Movement parameters (*x*, *y*, *z*, α, β, and γ) were then added as multiple regressors to the model to control for possible confounding effects of head movements. The generalized linear model parameters (β-values) were subsequently estimated (voxel-wise) for each participant. A linear combination of all predictors and estimated beta values was used to assess changes in BOLD response, and information about the overall percentages of signal change was saved in individual images.

Group-Level Analysis

Individual images were entered into a second-level effects analysis to perform a 2 (group: patients *vs.* controls) × 2 (imagination: alcohol-related vs. neutral) × 2 (picture: alcohol-related vs. neutral) analysis of variance (ANOVA). Statistics were carried out as whole-brain analyses with a significance threshold of $p \leq 0.05$. All findings were whole-brain (FWE) corrected at the peak level. As a

Table 1. Demographic and psychological variables of patients with AUD and the control group

	AUD group M (±SD)	Control group M (±SD)	Statistical parameters	*p* values
Age	45.46 (±10.06)	42.23 (±13.68)	$U = 96.50, Z = -0.77$	0.44
Education	12.85 (±1.68)	14.45(±2.40)	$F_{(df = 24)} = 0.63$	0.44
OCDS-G[a]	15.45 (±10.83)	2.08 (±2.07)	$F_{(df = 23)} = 14.96$	0.001**
HAMD	5.46 (±3.71)	1.38 (±1.39)	$F_{(df = 24)} = 21.62$	0.000***
	N	*N*		
Gender (m/f)	10/3	9/4	$\chi^2_{(df = 1)} = 0.20$	0.66
Nicotine (y/n)	7/6	9/4	$\chi^2_{(df = 1)} = 0.65$	0.42

Age and education are indicated in the years. $N = 26$ (13 patients with AUD and 13 healthy controls). AUD, alcohol use disorder; OCDS-G, Obsessive Compulsive Drinking Scale; HAMD, Hamilton Depression Rating Scale; y, yes; n, no. ** $p < 0.01$, *** $p < 0.001$. [a] One participant of the control group did not complete the OCDS-G (values are displayed for $n = 12$).

final step, a linear combination of all predictors and estimated beta values was used to assess changes in the BOLD response in each significant cluster. Significant interactions were followed up with post hoc tests (Welch's *t* test for small sample sizes) to assess beta value differences between the involved factor levels. A repeated measures ANOVA in SPSS investigated the main effects and interaction of the within factor "imagination type" (alcohol-related vs. neutral) and the between factors "group" (patients vs. controls) and "order" (alcohol-related imagination first vs. neutral imagination first). Visualization of all neuroimaging data was performed using xjview (extension toolbox, https://www.alivelearn.net/xjview/), talairach client (http://www.talairach.org/client.html), and self-written MATLAB scripts.

Results

Participant Characteristics

Table 1 summarizes the characteristics of the study participants. The results indicate that patients and controls did not differ significantly in terms of age and sex. As expected, the patient group had significantly higher scores on the HAMD and OCDS-G (confirming participants' enhanced craving for alcohol). No significant differences were found between the groups regarding education and smoking status. The majority of participants were right-handed (patients: 11 (right) versus 1 left; controls: 8 (right) versus 0 (left); for 6 participants this information is missing) with no differences between groups (Fisher's exact test $p = 1$). Only participants in the control group ($N = 13$) completed the AUDIT (score range 0–8) and BSI (GSI, *T* value range 24–45). These values corresponded to the absence of clinically relevant deviations.

Vividness

Subsequently, in the imagination task (T1), participants reported an overall high vividness after both imagination scenarios (see mean scores below), with no significant differences between the two groups (alcohol-related scenario: $M_{Patients} = 6.15$, $SD = 1.96$, $M_{Controls} = 7.33$, $SD = 2.31$, $U = 49.00$; $z = -1.62$, $p = 0.11$; neutral scenario: $M_{Patients} = 7.31$, SD = 1.66, $M_{Controls} = 7.62$, $SD = 1.86$, $U = 78.00$; $z = -0.34$, $p = 0.74$). After the cue-reactivity (T2) task, participants reported medium vividness scores regarding both imagination scenarios, again, no significant differences emerged between the groups (alcohol-related scenario: $M_{Patients} = 4.38$, SD = 1.98, $M_{Controls} = 6.08$, $SD = 2.74$, $U = 54.50$; $z = -1.31$, $p = 0.19$; neutral scenario: $M_{Patients} = 5.23$, $SD = 2.0$, $M_{Controls} = 5.69$, $SD = 2.84$, $U = 78.50$; $z = -0.31$, $p = 0.76$). The NRS score at T1 of one control subject was missing; otherwise, the data were complete.

Behavioural Data from Cue-Reactivity Task

Mean response time to question marks did not differ between patients and controls (controls: alcohol-related imagination: mean (M) = 511.89 ms, standard deviation (SD) = 98.17; neutral imagination: $M = 528.91$ ms, SD = 96.33; patients: alcohol-related imagination: $M = 492.22$ ms, SD = 150.84; neutral imagination: $M = 488.12$ ms, SD = 126.15), neither was a main effect of imagination task or a group by imagination task interaction observed (all $F < 0.6$; all $p > 0.45$). The groups did also not differ regarding errors (controls: alcohol-related imagination: median (Med) = 0, range: 0–6; neutral imagination: Med = 0, range: 0–0; patients: alcohol-related imagination: Med =

Table 2. Main effects of imagination and interaction effects of imagination × group on neurophysiological activation

Activated areas	MNI peak coordinate	Cluster size	*F* (1, 96)	*p* value
Main effect of imagination				
L thalamus	−8 −14 16	23	31.74	0.009
R thalamus	10 −16 18	18	30.00	0.016
R caudate body	10 2 18	7	27.47	0.037
L caudate head	−16 16 4	2	30.66	0.012
L caudate*	−4 2 18	2	27.20	0.041
L caudate body	−14 −8 22	1	26.70	0.048
Interaction effect of imagination × group				
R thalamus	12 −18 18	5	27.51	0.036
L caudate body*	−10 8 16	1	27.54	0.036

MNI, Montreal Neurological Institute; L, left; R, right. Regions were labelled using xjview software; *p* values (FWE-corrected on the peak level). * Region is labelled using the Talairach client, function: nearest grey matter.

0, range: 0–6; neutral imagination: median (Med) = 0, range: 0–5, all *z*-values between −0.45 and −2.1, all $p > 0.2$).

Neurophysiological Effects

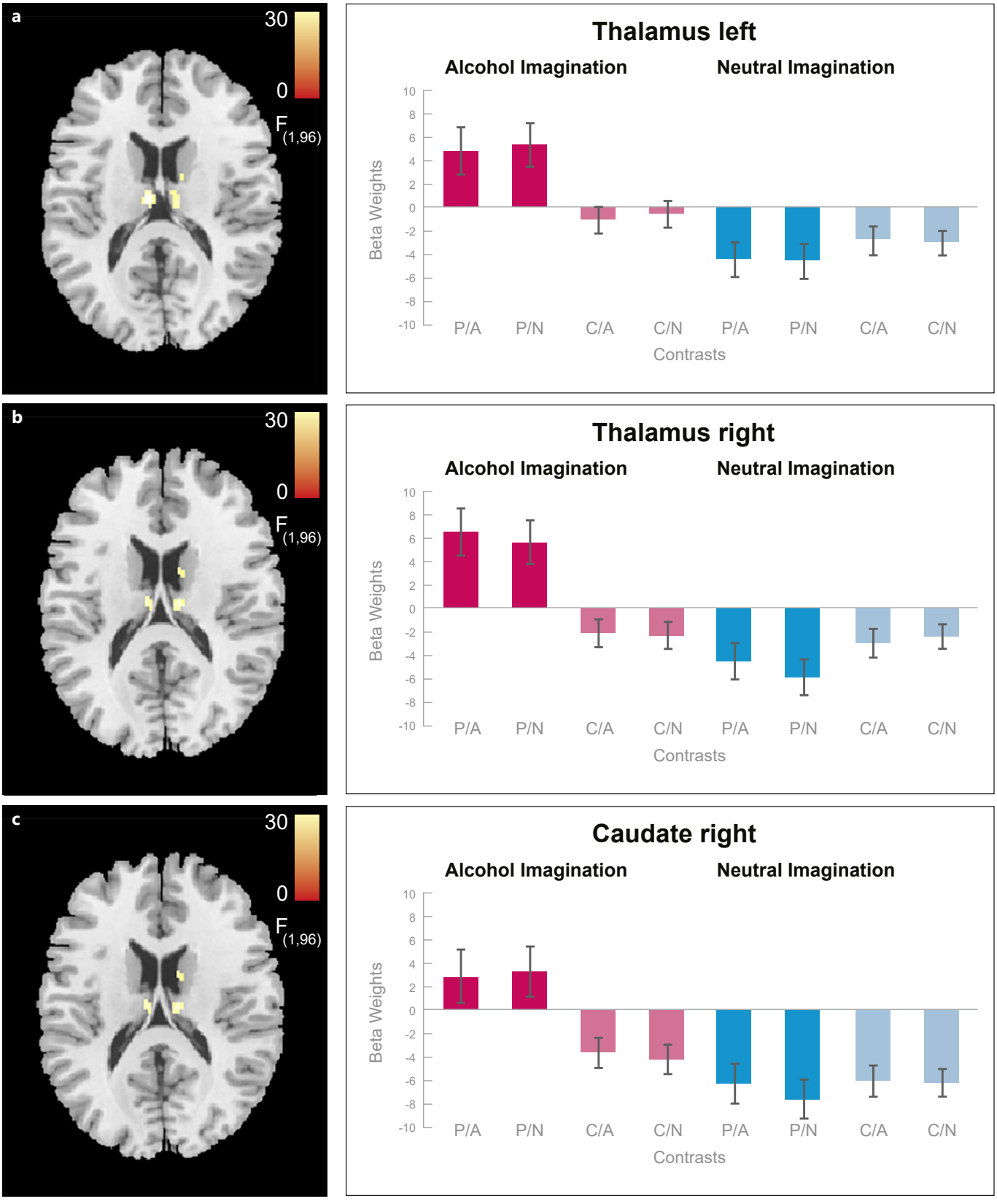
A 2 (group) × 2 (imagination) × 2 (picture) ANOVA was conducted to explore all potential effects of group (patients vs. controls), imagination (alcohol-related vs. neutral), and picture type (alcohol-related vs. neutral), as well as how their neurophysiological interaction correlates with cue reactivity. This analysis yielded a main effect of imagination and an interaction between groups and imagination (see Table 2). No other main effects or interactions were observed. The main effect of imagination revealed an increased BOLD signal during alcohol-related imagination (vs. neutral imagination) bilaterally in the thalamus and the right caudate nucleus, as well as very small clusters (<5 voxels) in the left caudate nucleus. Note that this contrast yielded no regions with higher activation during neutral imagination (vs. alcohol-related imagination). The significant interaction effect between imagination and the group was located in two clusters. One cluster was in the right thalamus, while the other, very small, cluster (1 voxel) was located in the left caudate body (shown in Fig. 2, 3).

Beta values per condition were extracted from the clusters where a significant main effect of imagination, or an interaction effect between imagination and group, was observed (shown in Fig. 2, 3). Following up on the interaction effect in the thalamus and the caudate nucleus, the Welch's *t* test indicated that in patients, activation was higher during alcohol-related (vs. neutral) imagination (thalamus: $t(74.30) = 15.88$, $p < 0.001$; caudate nucleus: $t(71.39) = 14.69$, $p < 0.001$), while no such effect was observed in the control group (thalamus: $t(33.48) = -0.35$, $p > 0.05$; caudate nucleus: $t(31.30) = -1.85$, $p > 0.05$). Additional analyses including the factor order indicated that results were not influenced by the order of the imagination task (alcohol-related imagination first vs. neutral imagination first).

Discussion

The present study aimed to explore the feasibility of an imagination task to simulate alcohol-related context effects during an fMRI assessment and to provide preliminary data on the neurophysiology of context effects and their interactions with cue-induced neural responses in patients with AUD. Our results indicate that participants were able to mentally evoke a vivid representation of an alcohol-related or neutral situation during the imagination procedure in the MRI scanner. As the vividness ratings did not differ between groups, the imagination was equally effective for patients and controls. Thus, an imagination procedure seems to be well suited to investigate contextual influences on brain activity. An imagination procedure offers a very high degree of individualization so that context effects can be simulated in an ecologically valid manner, a necessity that has been recently discussed in AUD research [36, 44, 53, 54].

The present pilot study observed higher neurophysiological activation after an alcohol-related imagination task in the right caudate nucleus and bilaterally in the thalamus. Even though this is a main effect of the imagination task, the beta values extracted per group and



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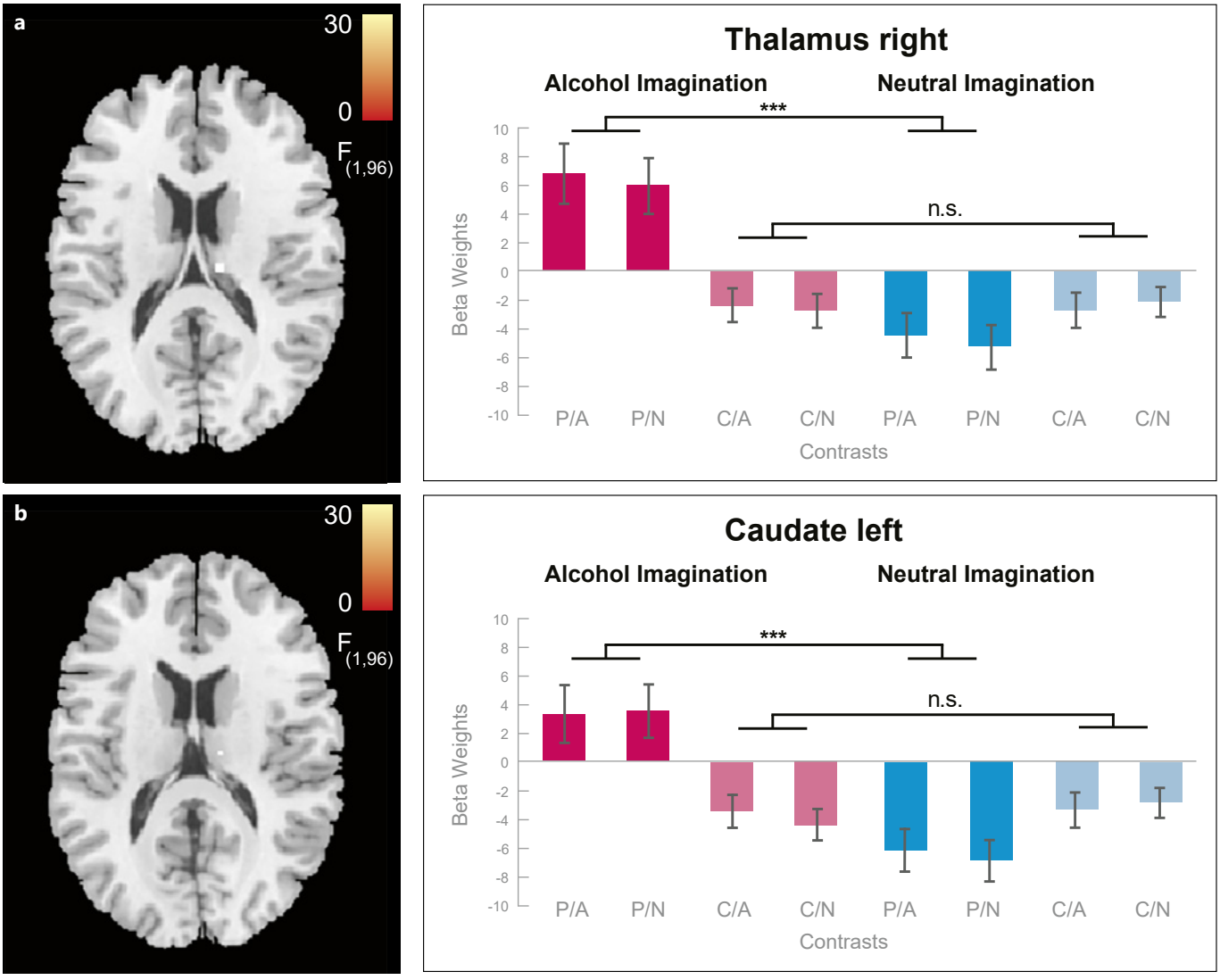

Fig. 3. Interaction effects of imagination × group. The brain areas depicting higher activation during alcohol-related imagination (vs. neutral imagination) in the patient group ($p < 0.05$, whole-brain FWE correction on peak-level, cluster size threshold = 0). **a** Cluster in the right thalamus (MNI 12 −18 18). **b** Cluster in the left caudate nucleus (MNI −10 8 16)) and beta weights per condition. Orientation of the anatomical images: left is left and right is right. P/A, patients with AUD, alcohol picture; P/N, patients with AUD, neutral picture; C/A, healthy controls, alcohol picture; C/N, healthy controls, neutral picture.

Fig. 2. Main effects of imagination. The brain areas depicting significantly higher activation during alcohol-related versus neutral imagination ($p < 0.05$, whole-brain FWE correction on peak-level, cluster size threshold = 0). **a**, **b** Cluster in the bilateral thalamus (MNI −8 −14 16 and 10 −16 18) and the right caudate nucleus (MNI 10 2 18) as well as beta weights per condition (**c**). Orientation of the anatomical images: left is left and right is right. P/A, patients with AUD, alcohol picture; P/N, patients with AUD, neutral picture; C/A, healthy controls, alcohol picture; C/N, healthy controls, neutral picture.

condition (Fig. 2, 3) suggest that it seems to be driven by the patient group displaying higher activation during the alcohol-related imagination task. But note that the interaction effect between group and imagination task was only significant in the right thalamus (and a very small cluster in the left caudate). The caudate nucleus (as part of the striatum) and the thalamus have repeatedly been discussed in the cue-related literature [21, 25], where cue-induced activity increases in both of these regions have been linked to addiction severity [55]. Among other structures, the caudate nucleus is involved in habit learning [56, 57] and compulsive behaviours [58]. The thalamus is generally involved in the relay of sensory information and attentional processing [59], and its activity in patients with AUD following alcohol-related cue exposure has been observed in different studies [26, 52].

Interestingly, when cocaine users were shown drug cues during either a neutral or a stress-inducing imagination, brain activation in the caudate nucleus and the thalamus correlated with subjective stress ratings and, in the caudate nucleus, also correlated with stress-induced cravings [23]. In addition, in non-clinical social drinkers, striatal activity increased after the imagination of alcohol-related versus neutral situations [44]. The results of our pilot study expanded these findings to recently abstinent inpatients with AUD, where we observed increased activity during alcohol-related imagination in the caudate nucleus. It seems that exposure to an alcohol-related context (i.e., to a "typical" drinking context) led to an increase in patients' neuronal reaction, which is reflected by the enhanced thalamic and caudate activation. This may indicate that automated, habitual responses, the relay of sensory information, and attentional resource allocation are intensified in patients while in this state.

Of note, no main or interaction effects of isolated cues (as presented in the cue-reactivity paradigm) were observed in the present study. One explanation for this unexpected null result might be the limited power due to a small sample size. If testing at a clearly to liberal threshold ($p_{(\text{uncorrected})} = 0.05$), first small clusters in regions typically observed in cue-reactivity paradigms [21] can be observed (mediofrontal or occipital activation, precuneus), but only when the threshold is lowered even further ($p_{(\text{uncorrected})} = 0.1$), activation encompasses regions more central to cue reactivity (PCC, middle cingulate, bilateral caudate, globus pallidus, insula, parahippocampal gyrus). It can thus not be ruled out that our study was underpowered to detect these effects. Another reason for the null results might be that the pictures used here did not trigger strong enough reactions, maybe because picture sets were not tailored to the participants' drink of choice [60]. Note, however, that former studies, having used the same stimulus set, were able to detect cue-reactivity effects in the EEG signal [61] or interactions between cue-type and an inhibitory task in fMRI [62] as well as in EEG studies [63]. In view of the relatively strong effect of context, a third reason for the non-effects of picture type might be attributed to the task. In the present study, the imagination procedure evoked an individually meaningful context, whereas the picture-type effect was operationalized by a series of unrelated, not personalized cues. Consistent with the levels of processing framework [64], the contents of the imagination, involving emotionally meaningful aspects embedded in a complex associative network of prior experiences and knowledge, will be processed at a deeper level and will draw more processing resources than the series of unrelated cues. Furthermore, research from various approaches has shown that contextual influences shape the processing of isolated stimuli [65, 66], including the possibility that contextual influences can dampen the influence of discrete stimuli [4].

If future studies confirm such an explanation, which attributes the failure to observe a picture-type effect to the imagination procedure, this would argue against combining an imagination procedure with a classical cue-reactivity paradigm, while at the same time corroborating the imagination's potential to simulate contextual influences during neurophysiological research. Future studies with larger samples should test, if picture-type effects are observable in the context of imagination procedures when pictures are tailored to the participants' drink of choice and sample sizes are large enough to guarantee adequate statistical power.

Overall, the present findings support the importance of multimodal contextual influences. As some authors have already called for an integration of contextual factors into existing cue-exposure training protocols [67], imagination procedures (such as the one used in this study) may be a useful way to implement this into practice [68]. By developing individualized scripts, which include very specific information about important contextual factors, such as sensory perceptions, emotions, thoughts, and social interactions, patients can be systematically exposed to complex context in which they are most likely to relapse.

This study has some limitations. The heterogeneity of patients' symptom manifestations in combination with a

small sample size may have led to a high variation in beta weights, making the detection of statistically significant effects more difficult. While the high diversity can be seen as a fundamental asset of this study (as our sample closely reflects the true clinical picture of AUD), a larger sample size may be useful to enhance statistical power and to test the influences of other more relevant variables (such chronicity, severity, comorbidities, or prior hospitalizations). Of note, some of the reported clusters (especially those in the left caudate nucleus) are rather small and should therefore be interpreted very cautiously. A larger sample size might also help to enhance statistical power (see online suppl. eTable 1; for all online suppl. material, see www.karger.com/doi/10.1159/000525435, SOM) and lead to more robust effects yielding larger clusters. Future studies should therefore focus on increasing the sample size to increase the translational utility. Furthermore, personalization of the stimulus material, such as using images of specific drinks on the basis of each individual's preference, may make cue-exposure sessions more salient [69], which may assist in the detection of potential cue-induced activations.

To the best of our knowledge, this is one of the first studies to investigate contextual influences simulated with an imagination procedure (alcohol-related and neutral) using a cue-reactivity task (alcohol-related and neutral stimuli) during an fMRI recording in inpatients with AUD and healthy controls. Taken together, our findings demonstrate the feasibility of an imagined procedure inside an MRI scanner in patients with AUD. Next to the scanner compatibility, the high level of personalization that can be achieved poses a major advantage of an imagination technique. Participants reported high vividness of the imagined scenarios and demonstrated the utility of such imagination procedures for neuroscientific research, as the different contexts induced by the imagination procedure showed considerable effects on the neuronal level. Interestingly, these context effects were stronger than any potential stimulus-type effects. Regarding the refining of intervention programs, such findings underline the importance of embedding therapeutic sequences in an individualized, subjectively relevant, alcohol-related context, as it may be achieved by, for example, imagination procedures or in vivo exposure.

Taken together, the present pilot study suggests that an alcohol-related context increases brain activation in the thalamus and the caudate nucleus, and that this effect is stronger in patients with AUD when compared to controls. These context-dependent effects are located in structures involved in habit learning, sensory relay, and attentional processing and provide evidence for the context dependency of neurophysiological responses in AUD. Future research might clarify the reasons for the failure to observe a picture-type effect and test whether this can be resolved by increasing statistical power and individualizing picture sets, or if an imagination procedure interferes with the evocation of picture-type effects. If the latter is the case, imagination procedure might not be useful in combination with a classical cue-reactivity paradigm, but rather as a stand-alone procedure to investigate contextual influences. Imagination procedures provide a feasible and valuable way to integrate these important contextual effects in neuroscientific designs, thereby enhancing the external validity and translational utility of neuroscientific research.

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Statement of Ethics

The study protocol was approved by the Ethics Committee of the Canton Bern (KEK), Bern, Switzerland (KEK decision #: 12/06). The authors have no ethical conflicts to disclose. All participants provided written informed consent.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Werner Fey, Maria Stein, and Franz Moggi designed the study. Werner Fey and Maria Stein implemented the study and supervised data collection. Frauke Conring, Andrea Federspiel, Leonie Steiner, Werner Fey, and Maria Stein performed the data analysis and contributed to the interpretation of the data. Werner Fey wrote the first draft of the manuscript, in collaboration with Frauke

Conring, Maria Stein, and Franz Moggi. Werner Fey, Frauke Conring, Andrea Federspiel Leonie Steiner, Franz Moggi, and Maria Stein revised the work critically and contributed to and approved the final manuscript. Werner Fey, Maria Stein, and Franz Moggi agree to be accountable for all aspects of the work.

Data Availability Statement

Data cannot be made available, as no consent in this respect was obtained from participants. Further enquiries can be directed to the corresponding author.

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