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Neurophysiological correlates of alcohol-specific inhibition in alcohol use disorder and its association with craving and relapse

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HIGHLIGHTS

- Craving affects the neurophysiological difference between alcohol-specific and neutral inhibitory control.
- Neurophysiological correlates of inhibition allow to distinguish between patients who relapse and those who remain abstinent.
- Event-related potentials of relapsers differ between alcohol-specific and neutral inhibition while those of abstainers do not.

ABSTRACT

Objective: This study investigates neurophysiological correlates of general and alcohol-specific inhibitory control in patients with Alcohol Use Disorder (AUD), focusing on its association with individual craving levels and with relapse at three-month follow-up.
Methods: 59 abstinent AUD patients and 20 healthy controls performed a Go/NoGo task incorporating alcohol-related and neutral stimuli during 64-channel electroencephalography (EEG) recording, yielding four event-related potentials (ERP) per participant (NoGo-Alcohol, Go-Alcohol, NoGo-Neutral, Go-Neutral). Whole-scalp randomization-based statistics assessed effects of the factors group (patients/controls or relapsers/abstainers), craving level, response type (NoGo/Go) and picture type (alcohol/neutral) on topography and signal strength of the ERP components N2 and P3.
Results: No differences on group level were observed between patients and controls. However, analyses incorporating individual craving indicated that the topographic difference between alcohol-related and neutral NoGo-N2 components increased with craving. Moreover, topographic differences in the alcohol-related and neutral NoGo-P3 component allowed for differentiation between relapsers and abstainers.
Conclusions: In alcohol-related contexts, the response inhibition conflict reflected in the NoGo-N2 seems enhanced in patients with high craving. The inhibition-sensitive NoGo-P3 varies in relapsers but not in abstainers between neutral and alcohol-related contexts.
Significance: In AUD patients, neurophysiological correlates of inhibition vary with alcohol-related contexts and craving, and might be indicative of relapse risk.

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1. Introduction

Given its high prevalence of over 3.3% (Prince et al., 2007) and an estimated 3–8% of all deaths being alcohol-related (Prince et al., 2007, Sudhinaraset et al., 2016), alcohol use disorder (AUD) is of very high relevance from a public health point of view and an immense burden for both those affected and their surroundings (Rehm et al., 2009). Despite evidence-based psychotherapeutic and pharmacological interventions, a remarkable percentage of AUD patients fail to achieve long-term improvement: Relapse rates of up to 85% in detoxified AUD patients without further treatment have been reported (Boothby and Doering, 2005, Walter et al., 2015), and evidence shows only slightly lower relapse rates for detoxifications that include psychotherapeutic interventions (Agarwalla et al., 2017). Yet, even after further long-term inpatient treatment, 20–80% of AUD patients resume drinking within 12 months after discharge (Weisner et al., 2003, Jin et al., 1998, Finney et al., 1999).Table 1C.

In the search for novel targets to reduce relapse rates in AUD, the dual-process model of AUD has increasingly gained interest. The model describes the imbalance between a fast affective-automatic system involved in the emotional evaluation of stimuli and appetitive responses and a slow reflective system linked to deliberate responses (Wiers et al., 2007). The development and maintenance of AUD is thought to derive from an increased affective-automatic system leading to heightened motivational qualities of alcohol and an impaired reflective system that impede to control short-term urges (Noël et al., 2010). The latter system includes inhibitory control, a key function of executive control, that is defined as the ability to stop, delay, or withhold a behavioral response (Logan et al., 1984). A 2014 meta-analysis including 18 AUD studies reported inhibitory control to be impaired in AUD (medium effect size; Smith et al., 2014), but several other studies did not observe such impairments on a behavioral level (e.g., Blanco-Ramos et al., 2019, Stein et al., 2018). Of special interest in AUD is the ability to execute inhibitory control in the presence of alcohol-related urges known as craving. Craving is not only one of the Diagnostic and Statistical Manual of Mental Disorders' (fifth edition DSM-5) criteria for AUD (American Psychiatric Association, 2013), but is also reported to impact cognitive processes such as inhibitory control. Specifically, it presumably reduces AUD self-control, and leads to an interference with the ability to inhibit responding (Gauggel et al., 2010). Therefore, executing inhibitory control in the presence of potentially craving-inducing alcohol cues in an everyday situation may be challenging for AUD patients. Thus, the investigation of inhibitory control with

Table 1
Comparison of demographics and alcohol-related variables in AUD patients and healthy controls.

	AUD patients (N = 59)	Controls (N = 20)	t or χ^2	p
DEMOGRAPHICS Sex				
male / female	38 / 21	13 / 7	0.002	0.96
Age				
Mean (SD)	43.47 (10.08)	44.70 (11.23)	−0.456	0.65
Range	24–60	27–58		
Years of education				
Mean (SD)	14.03 (2.67)	15.25 (3.11)	−1.690	0.10
Range	9–20	12–23		
Living situation			21.38	0.00
Alone	50.8%	0%		
With partner	35.6%	85.0%		
With parents	5.1%	0%		
With children	3.4%	0%		
With roommates	5.1%	15.0%		
Marital status			15.50	0.00
Single	55.9%	30.0%		
Married, living together	20.3%	60.0%		
Married, living separately	1.7%	0%		
Concubinate / in a serious relationship	0%	5.0%		
Divorced	22.0%	5.0%		
Employment			11.14	0.01
Yes, full-time	42.4%	65.0%		
Yes, part-time	18.6%	35.0%		
No	35.0%	0.0%		
ALCOHOL-RELATED VARIABLES				
AUDIT total score				
Mean (SD)	26.18 (5.67)	4.50 (1.99)	16.685	< 0.001
Range	13–38	1–7		
OCDS total				
Mean (SD)	8.42 (5.83)	3.55 (3.32)	3.537	< 0.001
Range	0–24	0–11		
OCDS compulsion				
Mean (SD)	3.95 (3.30)	2.50 (1.99)	2.346	<0.05
Range	0–15	0–7		
OCDS thoughts				
Mean (SD)	4.47 (3.21)	1.05 (1.76)	4.536	< 0.001
Range	0–14	0–5		
Years of AUD				
Mean (SD)	12.15 (8.92)	-	-	-
Range	0–35	-	-	-
# DSM-5 criteria of eleven fulfilled				
Mean (SD)	8.24 (2.00)	-	-	-
Range	4–11	-	-	-

Notes. Abbreviations: AUD: Alcohol Use Disorder; AUDIT: Alcohol Use Disorder Identification Test; DSM: Diagnostic and Statistical Manual of Mental Disorders; OCDS: Obsessive Compulsive Drinking Scale; SD: Standard deviation

respect to alcohol-related cues which could conceivably induce craving and hamper inhibitory abilities is of particular importance.

Inhibitory control is often assessed with the Go/NoGo task (GNG; Aragues et al., 2011). Within an alcohol-specific GNG, both alcohol-related and neutral stimuli are presented on a screen, prompting a motor response (Go trials). Occasionally, NoGo trials that necessitate the inhibition of such a response are included in the stimulus sequence. If an electroencephalogram (EEG) is recorded during a GNG task, two specific event-related potentials (ERP) have consistently been found to emerge in the NoGo trials: Firstly, the N2 component is characterized by a frontocentral negative peak between 200 – 300 ms after stimulus onset (Fallgatter and Strik, 1999) and is linked to conflict monitoring since amplitudes are highest when a response must be modulated (Donkers and van Boxtel, 2004). More precisely, it has been suggested that increased NoGo-N2 amplitudes reflect increased neurophysiological efforts to activate the inhibitory system while interrupting the preparations for a response execution (Géczy et al., 1999). The NoGo-N2 thus reflects the conflict between the urge to react to a stimulus and the task demand not to react to it in a NoGo trial. Lower N2 amplitudes in both Go and NoGo trials in AUD patients compared to controls have been found (e.g., Pandey et al., 2012). While NoGo-N2 components were furthermore shown to be attenuated in heavy compared to light drinkers (Oddy and Barry, 2009), other studies were unable to find such group differences (Petit et al., 2014, Stein et al., 2018, Kamarajan et al., 2005a). However, in subjects with strong craving, the conflict reflected in the NoGo-N2 was shown to be enhanced when inhibition had to be executed in alcohol-related contexts (Stein et al., 2018).

The second relevant component regarding response inhibition, the NoGo-P3, has a positive peak starting at 300 ms after stimulus onset (Bokura et al., 2001) and is interpreted as the neurophysiological correlate of actual inhibitory control execution (Smith et al., 2008). Topographically, the NoGo-P3 is maximal at frontocentral sites (Fallgatter and Strik, 1999). Previous studies on the NoGo-P3 have reported a decreased amplitude in patients compared to controls (e.g., Colrain et al., 2011, Stein et al., 2018, Kamarajan et al., 2005a, see also Luijten et al., 2014 for a review) but this was also observed occasionally in the Go-P3 (Kamarajan et al., 2005a), which favored a more general interpretation rather than an inhibition-specific one. It has even been reported in AUD offspring (Kamarajan et al., 2005b), suggesting an interpretation in terms of vulnerability. Other studies found no P3 differences (Fallgatter et al., 1998, Karch et al., 2007). One study even observed higher NoGo-P3 peaks and a higher NoGo-P3d (P3 difference waves NoGo minus Go) amplitude in AUD patients compared to controls. Within patients, this study reported that the P3d was higher in relapsing patients than in those managing to remain abstinent (Petit et al., 2014).

Alcohol-specific stimuli are highly salient in individuals with AUD due to neurobiological alterations following excessive alcohol consumption (Robinson and Berridge, 2001). Therefore, AUD patients attend to alcohol-related stimuli faster and longer (Field et al., 2014), and inhibition deficits are exacerbated for alcohol-related stimuli (Noel et al., 2007). Therefore, alcohol-related stimuli are likely to influence both the behavioral and neurophysiological processing in cognitive tasks, such as the GNG. Most studies investigating alcohol-consuming samples have indeed shown more inhibition errors in the presence of alcohol-related stimuli compared to neutral stimuli (Lannoy et al., 2018, Petit et al., 2012, Noel et al., 2007) as well as more alcohol-specific impairments in inhibitory control in binge compared to non-binge drinkers (Czapla et al., 2015). Yet, other studies did not observe such effects in heavy drinkers (e.g., Nederkoorn et al., 2009). Neurophysiologically, alcohol-related compared to neutral stimuli have been found to evoke higher NoGo-P3 (Fleming and Bartholow, 2014), higher NoGo-P3d (Campanella et al., 2019a) and higher NoGo-N2 (Korucuoglu et al., 2015, Fleming and Bartholow, 2014, especially in subjects with high craving: Stein et al., 2018). Furthermore, the increase in NoGo-P3d amplitudes compared between GNG measurements at the beginning and end of inpatient AUD treatment in response to alcohol-related but not neutral stimuli allowed for differentiation between abstainers and relapsers (Campanella et al., 2019a).

Taken together, alcohol-related stimuli may influence inhibitory processing, and alcohol-specific inhibition may be crucial in sustaining abstinence after treatment. In addition, craving has been reported to negatively impact cognitive processes such as inhibitory control (Gauggel et al., 2010) both on a behavioral (e.g., Lannoy et al., 2018, Noel et al., 2007) and a neurophysiological level (Stein et al., 2018). The present study thus investigates three research questions: First, it assesses potential differences in alcohol-specific inhibition between AUD patients and healthy controls on a neurophysiological level. Secondly, the association of individual levels of craving with the neurophysiology of alcohol-specific inhibition is examined. Based on a previous study (Stein et al., 2018), we hypothesized that increased craving would be associated with stronger N2 differences between alcohol-specific and neutral inhibitory control. Finally, the neurophysiological correlates of inhibitory control were related to a three-month follow-up period, contrasting AUD patients who had relapsed (i.e. "relapsers") with those who had remained abstinent (i.e., "abstainers"). We expected relapsers and abstainers to differ in the P3 component (Petit et al., 2014, Campanella et al., 2019a). Ultimately thriving towards a more individualized and ameliorated AUD treatment, it is crucial to boost the understanding of the interplay between inhibitory control and stimulus-induced craving as well as relapse (Campanella et al., 2019b, Czapla et al., 2016).

2. Methods

2.1. Participants

65 patients with AUD and 22 control subjects were included in this study. AUD patients were recruited at the beginning of their inpatient AUD treatment at two Swiss hospitals specialized in the treatment of AUD. The inclusion criteria for AUD patients were the primary diagnosis of AUD according to the DSM-5 and being between 18 and 60 years in age. Exclusion criteria were use of sedatives or opioids (e.g., heroin, methadone, benzodiazepines), the presence of another severe substance use disorder other than nicotine, insufficient German language skills, an acute somatic illness (e.g., flu), and a psychiatric axis-I disorder other than AUD as a primary diagnosis. All AUD patients had completed detoxification prior to treatment entry. Healthy controls were recruited through local advertisement and the study team's personal contacts and were matched according to AUD patients' age, gender, and years of education. Besides the same age and language requirement as in AUD patients, they were never to have been diagnosed with AUD, nor could they exceed seven points in the Alcohol Use Disorders Identification Test (AUDIT), which would indicate hazardous drinking (Babor et al., 2001). The study was approved by the local Swiss ethics committee (KEK-BE 2016–00998), and all subjects gave written informed consent prior to participation. Both AUD patients and healthy controls received monetary compensation for participation.

2.2. Procedure and questionnaires

One to two weeks after treatment onset, AUD patients filled out the Alcohol Use Disorder Identification Test (AUDIT; Babor et al.,

2001) questionnaire to assess alcohol-related problems, and completed sociodemographic questions. One week later, thus three weeks after treatment onset, patients completed the GNG task during which EEG was recorded. Healthy controls were invited to the EEG lab at one of the two clinics and filled out sociodemographic questionnaires, while completing the EEG measurement the same day. In a telephone screening prior to the EEG measurement, the AUDIT was queried in order to exclude individuals with an AUDIT score higher than seven.

On the day of the EEG measurement, AUD patients and controls filled out the German version of the Obsessive Compulsive Drinking Scale (OCDS; Mann and Ackermann, 2000) to assess for experienced craving during the seven preceding days. This scale yields an overall score as well as two subscales of cognitive and behavioral components of craving, thoughts and compulsion. Because the behavioral component of craving is key to a motor inhibition paradigm, the behavioral subscale OCDS compulsions (OCDS-C) was taken into account in the analyses. The OCDS's reliability and validity of the German version has been tested in a comparable sample of Swiss AUD patients undergoing residential AUD treatment and has revealed very high internal consistencies, high test–retest-reliabilities, and correlations of the OCDS subscales with AUD severity measures (Burren et al., 2012). Prior to the EEG measurement, all participants received GNG instructions : they were to press the left computer mouse button as fast as possible after having seen each presented stimulus, unless a stimulus appeared twice consecutively. After a short practice run with alcohol-unrelated stimuli (e.g., household items), all participants completed the GNG task, during which a 64-channel EEG was recorded. AUD patients commonly stayed in treatment for eight to twelve weeks. Three months after treatment discharge, they were sent questionnaires that included questions about their drinking behavior since discharge, i.e. if relapse had occurred or if they were able to abstain from drinking alcohol during the three months. Simultaneously, they were contacted by telephone and completed a short interview regarding drinking behavior since discharge.

2.3. Go/NoGo task (GNG)

Based on a previous study (Stein et al., 2018), a GNG task allowing to assess both alcohol-specific and neutral response inhibition was designed. Stimulus material of eight alcohol-related (ALC) and eight neutral (NEU) pictures of water were created under identical lighting standards, depicting well-known Swiss alcoholic beverages and water brands. Three alcohol-related picture sets (beer, wine, and spirits) were prepared, and each participant chose the most appealing alcohol type. Participants were instructed to answer as quickly and as accurately as possible and to press the left mouse button whenever a picture appeared on screen (Go trials), unless a stimulus was repeated twice in a row (NoGo trials), in which case they were to withhold from reacting and hence perform response inhibition (see Fig. 1). Each picture type (ALC, NEU) was presented 416 times as a Go stimulus and 64 times as a NoGo stimulus in a pseudorandomized order, with a minimum of five Go trials required to be between two NoGo trials. Each of the eight alcohol-related and water pictures used in an individual's GNG set appeared 60 times (52 times as a Go trial, eight times as a NoGo trial). Thus, there were 416 water Go trials, 416 alcohol Go trials, 64 water NoGo trials, and 64 alcohol NoGo trials. The task consisted of two blocks of 480 trials and lasted approximately 14 minutes. After half of the stimuli, participants could relax for up to two minutes, at which point they were encouraged to continue. The GNG incorporated a Go-NoGo ratio of 13:2, thus creating a strong prepotency to respond. Each picture was depicted for 900 ms, with an inter-stimulus interval of 100 ms. Participants were required to answer between the stimulus onset and the onset of the consecutive picture (0–1000 ms). The GNG task allowed to assess response inhibition not only in general, but also to differentiate between alcohol-related and neutral NoGo trials. The error of accidentally pressing the button despite a NoGo trial, known as an "error of commission" (EOC), is thought to reflect inhibitory control deficiency. Taken together, our GNG task involved four possible conditions: Go alcohol (Go ALC), Go neutral (Go NEU), NoGo alcohol (NoGo ALC), and NoGo neutral (NoGo NEU). The GNG was constructed, administered and recorded with E-Prime 2.0 (PST, Sharpsburg, PA).

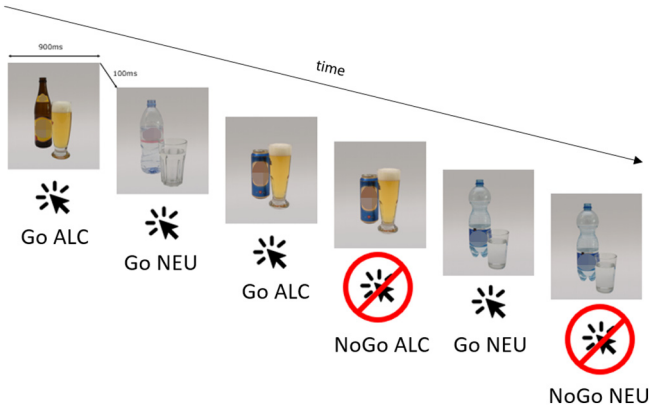

Fig. 1. GNG task to assess alcohol-specific and neutral inhibitory control. Notes. The GNG task incorporates alcohol-related and neutral stimuli in both Go and NoGo trials. Participants should press the left mouse button whenever a stimulus appears (Go), unless it was shown twice in a row (NoGo). Abbreviations: ALC: alcohol, NEU: neutral, ms: Milliseconds.

2.4. Statistical analyses of demographics, questionnaires, reaction times and error rates

Error rates revealing the extent of deficiency in inhibitory control were counted numerically as the responses on NoGo trials (i.e., errors of commission, EOC). The percentage and accuracy of EOC was calculated from a possible 64 (alcohol, neutral) or 128 (total) NoGo trials. Reaction times (RT) were analyzed by stimulus type for Go trials (Go Alcohol and Go Neutral), and the accuracy of correct Go trials was calculated from the possible 418 (alcohol, neutral) or 832 (total) Go trials. Independent t-tests (and χ^2 for gender distribution) for each GNG variable as well as group differences in demographics were calculated to investigate differences between the AUD and control group in SPSS 26 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp.).

2.5. Electrophysiological data

2.5.1. EEG data acquisition preprocessing and ERP computation

EEG was recorded with an EEG system (actiCHamp Plus (2019). Gilching, Germany: Brain Products GmbH) with 64 active electrodes positioned according to the extended 10/10 system (electrode impedances were kept below 20kΩ; band-pass filter 0.016–250 Hz; sampling rate of 500 Hz; online reference electrode FCz). The software BrainVision Analyzer (Version 2.2.0, Gilching, Germany: Brain Products GmbH.) was used to preprocess data (artefact removing) and for ERP computation. Eye movement and heartbeat artifacts were removed with an independent component analysis (ICA): defective or very noisy electrode data was interpolated, and remaining artifacts, such as episodes of strong movement, were removed manually. Data were filtered (0.5 to 18 Hz

band-pass filter IIR; 50 Hz notch filter, filter order 4) and re-referenced to average reference.

The ERPs for each picture type (ALC, NEU) and response type (NoGo, Go) were computed by averaging segments from −500 pre- to 1500 ms post-stimulus presentation. Subsequently, the following four ERPs were extracted: alcohol-related NoGo (NoGo ALC), neutral NoGo (NoGo NEU), alcohol-related Go (Go ALC), and neutral Go (Go NEU). Only artifact-free segments with correct behavioral responses were included in the ERP analyses, i.e. responses in Go trials and response inhibition in NoGo trials. Since a conscious motor reaction to a visual stimulus is highly unlikely in the 150 ms after stimulus onset (Shelton and Kumar, 2010), any response time below 150 ms post-stimulus was counted to be involuntary/premature and was excluded from the analysis in the Go trials. As every NoGo trial was preceded by the same picture (i.e., by a Go trial of the same stimulus type), Go trials that were included in the ERP computation were also required to be preceded by a Go trial of the same stimulus type. This procedure was chosen to parallel potential offset and preparatory components between Go and NoGo trials, so that these would be subtracted out by the computation of the difference waves. Thus, descriptive analyses of differences waves as well as statistical analyses incorporating the factor response type (and thus building on the difference waves) could not be systematically affected by these potentially interfering effects. A minimum of 20 correct and artifact-free segments per NoGo ERP (NoGo ALC and NoGo NEU) was required for each participant. The mean number of each ERP across patients and healthy controls was 136 (range: 52–172) for Go ALC, 134 (range: 67–156) for Go NEU, 43 (range: 24–63) for NoGo ALC, and 42 (range: 20–62) for NoGo NEU. Furthermore, to isolate inhibition-specific activation, difference waves (NoGo minus Go) were computed separately for each stimulus type (i.e. NoGo ALC minus Go NEU; NoGo NEU minus Go NEU) for each subject.

2.5.2. Statistical ERP analyses

ERP statistics concentrated on the N2 and P3 components as indicated by the Global Field Power (GFP) of the four different ERPs, with the earliest pre-N2 local minimum at approximately 170 ms and the latest post-P3 local minimum at approximately 750 ms. During this time interval, preprocessed ERP data were analyzed using whole-scalp randomization statistics with 5000 randomization runs as implemented in the free open-source software Randomization Graphical User interface (RAGU; Koenig et al., 2011). Significance of effects was tested at each time point. A duration criterion, with significant effects having to contain a minimum of ten consecutive time points, i.e. 20 ms, in order to be reported, was included to minimize false positives due to multiple testing (similar as in Rohde et al., 2018, Murray et al., 2004).

For each research question, a topographic analysis of variance (TANOVA) was conducted with normalized data to investigate topographic differences, and a Global Field Power (GFP) analysis with non-normalized data to investigate differences in overall amplitude. GFP, an index of the overall voltage differences across all 64 channels, reflects overall signal strength (Lehmann and Skrandies, 1980). TANOVA analyses allow to test whether the different experimental conditions elicit different map topographies and thus differ in underlying functional brain states (Habermann et al., 2018). When testing whether map topographies vary systematically with a continuous predictor, such as craving in these analyses, a special type of TANOVA, a topographic analysis of covariance (TANCOVA) was conducted (Koenig et al., 2008). In the TANCOVA, the strength of covariance between each electrode and craving is calculated and summarized in a covariance map. The better these values covary, the larger the GFP of this covariance map is. The value of this GFP is then tested for significance through randomization statistics, i.e., by comparing it against the value obtained in 5000 randomization runs.

Brain electric activity related to alcohol-specific inhibition in AUD patients was the primary focus of this study. Therefore, all analyses were conducted to identify either significant three-way interactions (including the within-factors stimulus type (alcohol, neutral) and response type (NoGo, Go) and the respective between-factor (group or craving)), or significant two-way interactions between the factor response type (NoGo, Go) and the respective between-factor. Note that statistical effects in these interactions cannot be contaminated by the offset components as they involve the factor response type (and thus difference maps subtracting Go from NoGo trials, where the offset components are cancelled out). Such significant interactions were followed up by testing effects on the respective factor levels separately (e.g., NoGo or Go only, alcohol or neutral stimuli only, patients or controls only, and relapsers or abstainers only). All other main effects and interactions will be reported but not discussed in detail.

Relating to our three research questions, the three specific ERP analyses were the following: The aim of the first analysis was to compare AUD patients and healthy controls in terms of the neurophysiological processing of inhibitory control. Thus, it included the categorical between-factor group (patients, controls), and the within-factors response type (NoGo, Go) and picture type (alcohol, neutral). The second analysis investigated the interaction between the continuous factor compulsive craving (OCDS-C) as between-factor and the within-factors response type (NoGo, Go) and the stimulus type (alcohol, neutral) in all subjects. This allowed for investigation of whether the extent of craving influenced the neurophysiology of inhibition in an alcohol-related context. The third analysis addressed whether AUD patients who had relapsed (“relapsers”) and those who were able to remain abstinent (“abstainers) in the three months after discharge differed in their ERP response during alcohol-specific inhibition. The analysis included the categorical dichotomized between-factor relapse/abstinent and the within-factors response type (NoGo, Go) and stimulus type (alcohol, neutral).

2.5.3. sLORETA source analyses

Generators for selected significant topographic effects were estimated with sLORETaA source analysis (Pascual-Marqui, 2002). Because statistical significance was already established on the scalp level, an uncorrected alpha level of 0.05 was assumed.

3. Results

3.1. Sample description

We included 59 AUD patients and 22 healthy controls in the analyses. As can be seen in table 1, the groups did not differ in terms of sex, age, and years of education, but did significantly differ in AUDIT, OCDS total, OCDS compulsion (OCDS-C), and OCDS thoughts scores, marital status, living situation, and employment. The following medication was used by the AUD sample: Vitamins: 75.6 %; Antipsychotics as used in substance use disorders: 15.3 %; Antidepressants: 39.0 %; Plant-based relaxants: 17.0 %; Psychostimulants: 1.7 %; Other psychopharmacological medication, e.g., Antiepileptics: 6.8 %; other somatic medication: 57.6 %; Drugs specifically used for alcohol dependence: 3.9 %. One AUD patient did not take any medication. As for other psychiatric diagnoses in the chapter F in the 10th edition of the International Statistical Classification of Diseases and Related Health Problems (ICD-10), AUD patients were diagnosed with the following besides F10.x (alcohol dependence): F1 Mental and behavioral disorders due to psychoactive substance use: 74.6 % tobacco and 35.6 % another

substance (currently abstinent and a value below 25 in the Drug Use Disorders Identification Test (DUDIT)); 0 % F2 Schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders; 49.2 % F3 Affective disorders; 8.5 % F4 Anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders; 1.7 % F5 Behavioral syndromes associated with physiological disturbances and physical factors; 3.4 % F6 Disorders of adult personality and behavior; 5.1 % Behavioral and emotional disorders with onset usually occurring in childhood and adolescence.

Of the initially measured 65 AUD patients and 22 healthy controls, two AUD patients were excluded from analysis due to more than 50% Errors of Commission, indicating they may have not understood the task or were too slow in processing the fast-paced GNG task. Two AUD patients and two controls were excluded because they had fewer than 20 correct NoGo ERPs in at least one stimulus type, and finally, another two AUD patients were excluded due to defective EEG data, resulting in fewer than 20 artifact-free trials. Thus, the final sample consisted of 59 AUD patients and 20 healthy controls.

3.2. GNG performance and ERP results in AUD patients and controls

3.2.1. GNG performance

AUD patients showed slower reaction times in Go trials compared to controls in the alcohol-related, neutral, or combined context, but these differences were not significant (see table 2). The groups did not differ regarding percentage of errors of commission (EOC) in the alcohol-specific, neutral, or combined context. All relevant results can be found in table 2.

3.2.2. ERP results

The focus of this study being (alcohol-specific) inhibition in AUD patients, we focused either on significant three-way interactions (stimulus type (ALC, NEU) × response type (NoGo, Go) × the respective between-factor (group or craving)) or significant two-way interactions including the factor response type (NoGo, Go) and the respective between-factor. While such significant interactions are followed up in more detail as reported in the paragraphs titled "effects involving (alcohol-specific) inhibition", all other main effects and interactions are only briefly reported for completeness in the paragraphs titled "other effects".

3.2.2.1. ERP results with group as between-factor: Are there differences in the neurophysiology of (alcohol-specific) inhibition between AUD patients and healthy controls?. Comparison of AUD patients and healthy controls with the between-factor group (AUD patients, healthy controls) and within-factors response type (NoGo, Go) and picture type (ALC, NEU):

TANOVA: ***Effects involving (alcohol-specific) inhibition:*** Neither a significant three-way interaction nor a significant response type × group interaction was found. ***Other effects:*** A very long main effect of response type was found throughout the complete analyzed time period ($p < .05$), indicating that the GNG task achieved the goal of evoking differential activation in NoGo trials. Also observed were a main effect of picture type (170 ms to 382 ms), significant response type × picture type interactions (294–316 ms; 366–410 ms; 442–470 ms; 674–750 ms; all $p < .05$), and a group main effect (724 ms extending beyond our analysis window of 750 ms, $p < .05$).

GFP: ***Effects involving (alcohol-specific) inhibition:*** In terms of GFP, no significant three-way interaction or response type × group interaction was found. ***Other effects:*** A significant picture type × group interaction was found in a late P3 time frame between 630 and 676 ms ($p < .05$). Alcohol-specific stimuli elicited more GFP than neutral stimuli in AUD patients, whereas the opposite was the case for controls. A significant time frame was found for the response type × picture type interaction between 276 and 300 ms ($p < .01$). NoGo ALC and NoGo NEU elicited almost twice as much GFP compared to the according Go ERP, with NoGo NEU eliciting even slightly more than alcohol. Just as in the TANOVA analysis, a very strong main effect of response type (NoGo, Go) was found throughout the complete analyzed time period. While no main effect of group was found, a main effect of pic-

Table 2
Behavioral parameters of inhibitory control performance in AUD patients and healthy controls.

	AUD patients (N = 59)	Controls (N = 20)	t	p
PERCENTAGE EOC / ACCURACY IN NOGO TRIALS				
NoGo ALC				
EOC in %	22.51 (12.50)	25.47 (10.38)	−0.95	0.34
Range	1.56–50.00	10.94–46.88		
Accuracy in %	77.49 (12.50)	74.53 (10.38)		
NoGo NEU				
EOC in %	26.54 (13.73)	27.81 (9.45)	−0.39	0.70
Range	3.12–59.38	17.19–54.69		
Accuracy in %	73.47 (13.73)	72.19 (9.45)		
NoGo total				
EOC in %	24.52 (12.42)	26.64 (9.38)	−0.70	0.49
Range	2.3 – 49.2	16.4 – 47.7		
Accuracy in %	75.48 (12.42)	73.36 (9.38)		
REACTION TIMES (RT) / ACCURACY IN GO TRIALS				
Go ALC				
Mean RT in ms (SD)	411.03 (49.47)	387.79 (46.75)	1.84	0.070
Accuracy in %	98.42 (1.41)	98.29 (1.24)	0.36	0.72
Range	90.4 – 99.5	95.2 – 99.5		
Go NEU				
Mean RT in ms (SD)	406.84 (49.78)	383.19 (42.93)	1.90	0.06
Accuracy in %y	98.45 (1.49)	98.87 (0.63)	−1.25	0.22
Range	90.7 – 99.5	96.9 – 99.5		
Go total				
Mean RT in ms (SD)	408.94 (49.33)	385.47 (44.58)	1.88	0.06
Accuracy in %	98.43 (1.40)	98.58 (0.88)	−0.45	0.66
Range	90.6 – 99.5	96.5 – 99.5		

Notes. For NoGo trials, the t and p value are the same for % EOC and accuracy and are only written out for % EOC. AUD: Alcohol Use Disorder; EOC: Errors of commission; SD: Standard deviation. Abbreviations: ALC: Alcohol; AUD: Alcohol Use Disorder; EOC: Errors of Commission; RT: Reaction time; SD: Standard deviation.

ture type between 384 and 450 ms ($p < .05$), with alcohol-specific stimuli eliciting more GFP than neutral stimuli, was found.

3.2.2.2. ERP results with compulsive craving (OCDS-C) as between-factor: Are individual levels of craving associated with the neurophysiology of alcohol-specific inhibition?. Analysis with craving (OCDS-C) as the between-subjects factor and the response type (NoGo, Go) and picture type (ALC, NEU) as the within-subjects factors:

TANCOVA: *Effects involving (alcohol-specific) inhibition:* A significant three-way interaction (craving × response type × picture type) in the N2 time frame (212–248 ms, $p < .01$) was yielded in the whole group (AUD patients and controls combined). Follow-up analyses in this time frame indicated that this three-way interaction was driven by the NoGo trials, in which the difference between alcohol-related and neutral NoGo trials significantly increased with craving, while no such interaction could be observed in the respective analysis of Go trials. To test whether the here-described effect is relevant to AUD, we repeated the analysis in AUD patients only, where the significant three-way interaction was replicated (222–246 ms, $p < .05$), while a respective analysis in controls yielded no significant results. As an illustration of the here-described interaction, the covariance maps (NoGo ALC; NoGo NEU), which depict how strong and in which direction each electrode covaries with the amount of craving, were subtracted from each other (NoGo ALC minus NoGo NEU) to create a covariance difference map (Fig. 2A). This covariance difference map thus indicates how strong and in which direction each electrode covaries with craving in alcohol-related NoGo-trials while accounting for the respective activity during neutral NoGo-trials. It therefore depicts the electrophysiological activation which varies with craving selectively during alcohol-related NoGo-trials. In individuals with higher craving, the difference between NoGo ALC and NoGo NEU, as depicted in the covariance difference map, was stronger: The higher the craving, the stronger the negativity observed at frontal electrodes (and the positivity at left parieto-temporal electrodes) during alcohol-related NoGo-trials. As a visualization of this relationship, the amount of overlap between the covariance difference map and the individual difference ERPs (NoGo ALC minus NoGo NEU) was quantified by fitting the covariance difference map (i.e. applying a spatial filter) to the individual ERPS. This fit is plotted against the individual craving values in Fig. 2B, indicating how the difference between alcohol-related and neutral NOGO-trials increased with craving.

In order to estimate generators of this effect, the paired contrast (alcohol-related minus neutral NoGo-trials) was correlated with the OCDS-values in sLORETA, yielding brain regions in which the activation increased with craving selectively during alcohol-related (but not during neutral) NoGo-trials. Using a cut-off of $r = 0.187$, corresponding to an alpha level of 0.05 (uncorrected, one-tailed), this analysis yielded four right-sided clusters (see Fig. 2C) in anterior cingulate gyrus (BA 24, 32), medial frontal gyrus (BA 6, 8), inferior parietal lobule (BA 40) and middle/inferior temporal gyrus (BA 39, 19).

A two-way interaction between response type and craving was also found in the P3 time frame between 390–426 ms ($p < .05$).

Other effects: As reported above, the main effect of response type is evident throughout the complete time frame, but no main effect of craving was found. A significant main effect of picture type was found between 170–384 ms, and several timeframes in the picture type × response type interaction were also significant (294–316 ms; 366–410 ms; 442–470 ms; 672–750 ms, all $p < .05$).

GFP: *Effects involving (alcohol-specific) inhibition:* In AUD patients and controls combined, no significant three-way interaction or response type × craving interaction was found. ***Other effects:*** No picture type × craving interaction nor craving main effect was found. A significant response type × picture type interaction occurred between 274 and 300 ms ($p = .01$). As expected, NoGo trials elicited higher GFP than Go trials. Besides the consistent finding of a very strong main effect of response type throughout the complete analyzed time period, a main effect of picture type was found between 384 and 450 ms ($p < .05$), with alcohol-specific stimuli generally eliciting more GFP than neutral stimuli.

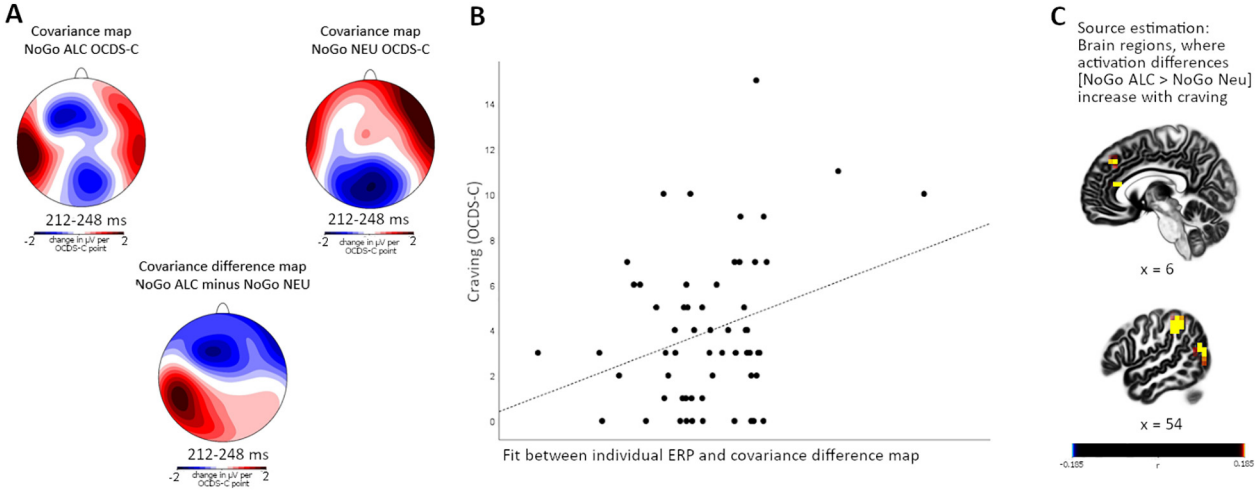

Fig. 2. Craving and picture type interaction in the NoGo-N2 component. 2A: OCDS-C covariance maps for the N2 effect (212–248 ms). The color coding in the covariance maps indicates how strong and in which direction activation at each electrode varies with the amount of craving (in microvolts (μV) per point on the OCDS-C scale). Upper left: NoGo ALC covariance map: Topography in NoGo ALC ERP, found to vary with OCDS-C. Upper right: NoGo NEU covariance map: Topography in NoGo NEU ERP, found to vary with OCDS-C. Bottom: Covariance difference map calculated by subtracting the covariance maps above (NoGo ALC minus NoGo NEU). The higher the craving, the more accurately the individual ERPs are described by the here depicted covariance map. Thus, in subjects with high craving, the N2 in NoGo ALC trials (but not in NoGo NEU trials) is characterized by stronger negativity at left frontal electrodes and stronger positivity at left parieto-temporal electrodes. This difference between NoGo ALC trials and NoGo NEU trials increases with craving and is less pronounced in subjects with lower craving. 2B: The presence of the covariance difference map in the individual difference ERPs (NoGo ALC minus NoGo NEU) increases with craving. Individual craving values are plotted against a fit between individual ERP data and the covariance difference map. 2C: Generators of the N2 effect. Regions, in which activation during alcohol-related NoGo trials increased with craving, include the anterior cingulate gyrus and medial frontal gyrus (both shown above) as well as the inferior parietal lobule and the middle/inferior temporal gyrus (shown below) Abbreviations: ALC: Alcohol, NEU: Neutral, OCDS-C: Obsessive compulsive drinking scale, subscale compulsion, ms: Milliseconds, μV: Microvolt.

3.2.2.3. ERP results with relapse/abstinence as between-factor: Are the neurophysiological correlates of inhibition related to relapse?. Information on relapse/abstinence in the three months after discharge was obtained from 51 (86.4%) of the 59 participating AUD patients. Of these, 25 relapsed and 26 had remained abstinent in the three months after treatment discharge. No significant group differences between relapsers and abstainers were found in terms of AUDIT ($t(49) = 0.47$, $p = .64$), number of detoxifications ($t(49) = 1.22$, $p = .23$), years of AUD ($t(49) = 0.64$, $p = .53$), nor number of DSM-5 criteria ($t(49) = 0.47$, $p = .64$), but in craving (OCDS-C ($t(49) = -2.39$, $p = .02$)), with relapsers reporting significantly higher ($M = 4.80$ ($SD = 3.24$)) craving than abstainers ($M = 2.73$ ($SD = 2.95$)). Exemplary difference waves (NoGo-Go) isolating inhibition specific activity as well as exemplary single-channel waveforms are depicted in Fig. 3.

The dichotomous variable relapse/abstinence served as the between-subjects factor and the response type (NoGo, Go) and picture type (ALC, NEU) as the within-subject factors.

TANOVA: *Effects involving (alcohol-specific) inhibition:* A significant three-way-interaction in the P3 component between 516 and 538 ms ($p < .05$) was yielded. In the follow-up analysis of this P3 time frame among relapsers and abstainers separately, the two-way interaction between picture type and response type was found to be significant in relapsers ($p < .01$). In abstainers, this interaction was not significant ($p = .77$), interestingly, this null finding could also be observed in the control group in this same time frame ($p = .85$). As relapsers were thus the only group with a significant response type by picture type interaction, the next analysis focused on relapsers and compared the effects of picture type in Go and NoGo ERPs separately. Here, the effect of picture type was significant for both Go and NoGo ERPs ($p < .05$), but the pattern of topographic difference varied with response type as can be seen in the alcohol-minus-neutral difference maps for NoGo and Go trials in Fig. 4. The same analyses in abstainers yielded no significant effects ($p = .91$ in NoGo; $p = .79$ in Go). The topography of the four ERPs and difference maps in relapsers and abstainers are shown in Fig. 4. In NoGo trials, relapsers showed more negativity in right-sided frontal electrodes in alcohol compared to neutral trials, whereas in Go trials, the opposite pattern occurred. Here, in right frontal-sided electrodes, there was more positivity frontally in alcohol-related trials compared to neutral trials. Thus, while the picture type seemed to affect the topography of Go and NoGo ERPs differently in relapsers, this could not be found in abstainers.

To be complete, when testing effects of response type (NoGo, Go) separately for each picture type and in each group, all of these analyses yielded a significant effect of response type (all p values < 0.05): In both abstainers as well as relapsers, Go and NoGo trials differed topographically in both ALC and NEU trials. When analyzing the effects of group (abstainers, relapsers) and response type (NoGo, Go) separately for ALC and NEU trials, both analyses yielded a significant main effect of response type, but no response type × group interaction. Testing the effects of group (abstainers, relapsers) and picture type (ALC, NEU) separately for NoGo and Go trials, no significant main effects or interactions were yielded.

Other effects: Apart from the significant main effect of response type throughout the complete time frame ($p < .05$), a significant picture type main effect was found between 170–204 ms and 236–298 ms, as well as three significant picture type × response type interaction time frames (364–412 ms; 446–468 ms; 694–750 ms; all $p < .05$). While no relapse main effect was found, a significant picture type × relapse interaction between 728–748 ms ($p < .05$) was.

GFP: *Effects involving (alcohol-specific) inhibition:* No significant three-way interaction was found, nor were any two-way interactions, or relapse main effect. ***Other effects:*** Besides the strong main effect of response type throughout the complete analyzed time period, one picture type main effects were found (626 – 666 ms; $p < .05$). As in the other main effects of picture type, alcohol-specific stimuli elicited more GFP than neutral stimuli.

4. Discussion

The present study investigated the neurophysiology of alcohol-specific inhibition in recently abstinent AUD patients as assessed with ERPs during a GNG task measuring alcohol-specific as well as neutral inhibition. While a first analysis examined neurophysiological differences between AUD patients and healthy controls in alcohol-specific and neutral inhibition, it yielded no significant interactions of interest. However, when a second analysis assessed the interaction of individual levels of craving and inhibition type (alcohol, neutral), we observed that with high levels of craving, the neurophysiological difference in the N2 component between alcohol-specific and neutral inhibition increased. Finally, when dividing the group of AUD patients between those who remained abstinent during the three months after treatment discharge and those who relapsed, our data indicated that in abstainers, the picture type interacted with the response type in the P3 component, while no such effect was observed in abstainers or controls.

The non-significant results in terms of group differences between AUD patients and controls add to those studies that also fail to detect any differences in inhibition-specific neurophysiological activity between the groups (Fallgatter et al., 1998, Karch et al., 2007, Stein et al., 2018, but see Petit et al., 2014, Kamarajan et al., 2005a). However, when the analysis included individual craving values, a significant three-way interaction between craving, response type and picture type in the NoGo-N2 component was yielded. Follow-up analyses indicated that this interaction was driven by the NoGo trials, wherein the difference between alcohol-related and neutral NoGo trials increased with craving. Thus, in line with our hypothesis, after accounting for activation during neutral NoGo-trials, patients with higher craving had a higher relative increase in alcohol-related NoGo-N2, which was characterized by an increase of negativity in frontocentral electrodes selectively during alcohol-related NoGo trials. Source localization indicated that during alcohol-related NoGo-trials, brain activation in right anterior cingulate gyrus, medial frontal gyrus, inferior parietal lobule and middle/inferior temporal gyrus increased with craving. The NoGo-N2 component is thought to reflect the early neurophysiological state of the conflict monitoring between the urge to react to a stimulus (as in the Go trials) and the simultaneous requirement to withhold from such a reaction (in NoGo trials; Donkers and van Boxtel, 2004). Our results indicate that this early processing step requires additional neuronal resources during alcohol-related NoGo-trials in patients with high craving, possibly because the alcohol-related context leads to enhanced conflict when strong craving is experienced. This finding replicates an earlier study (Stein et al., 2018), which used a similar task and a comparable analysis strategy. Other than that, there is to the best of our knowledge only one further study that investigated inhibition-specific ERPs in AUD patients in relation to craving. Following a different approach, this study used the change in craving from pre- to post-detoxification as a covariate, but did not observe any effects (Campanella et al., 2019a). However, in non-clinical samples, studies have reported NoGo-N2 amplitude increases for alcohol-related stimuli (Fleming and Bartholow, 2014, Korucuoglu et al., 2016) as well as food stimuli (Wolz et al., 2017) and have also linked these effects to craving (Wolz et al., 2017) or alcohol-sensitivity (Fleming and Bartholow, 2014). The finding that the conflict–sensitive NoGo-N2 is impacted by the stimulus type in participants with higher craving bears clinical relevance because it indicates that this enhanced conflict might be a potentially important target for therapeutic interventions.

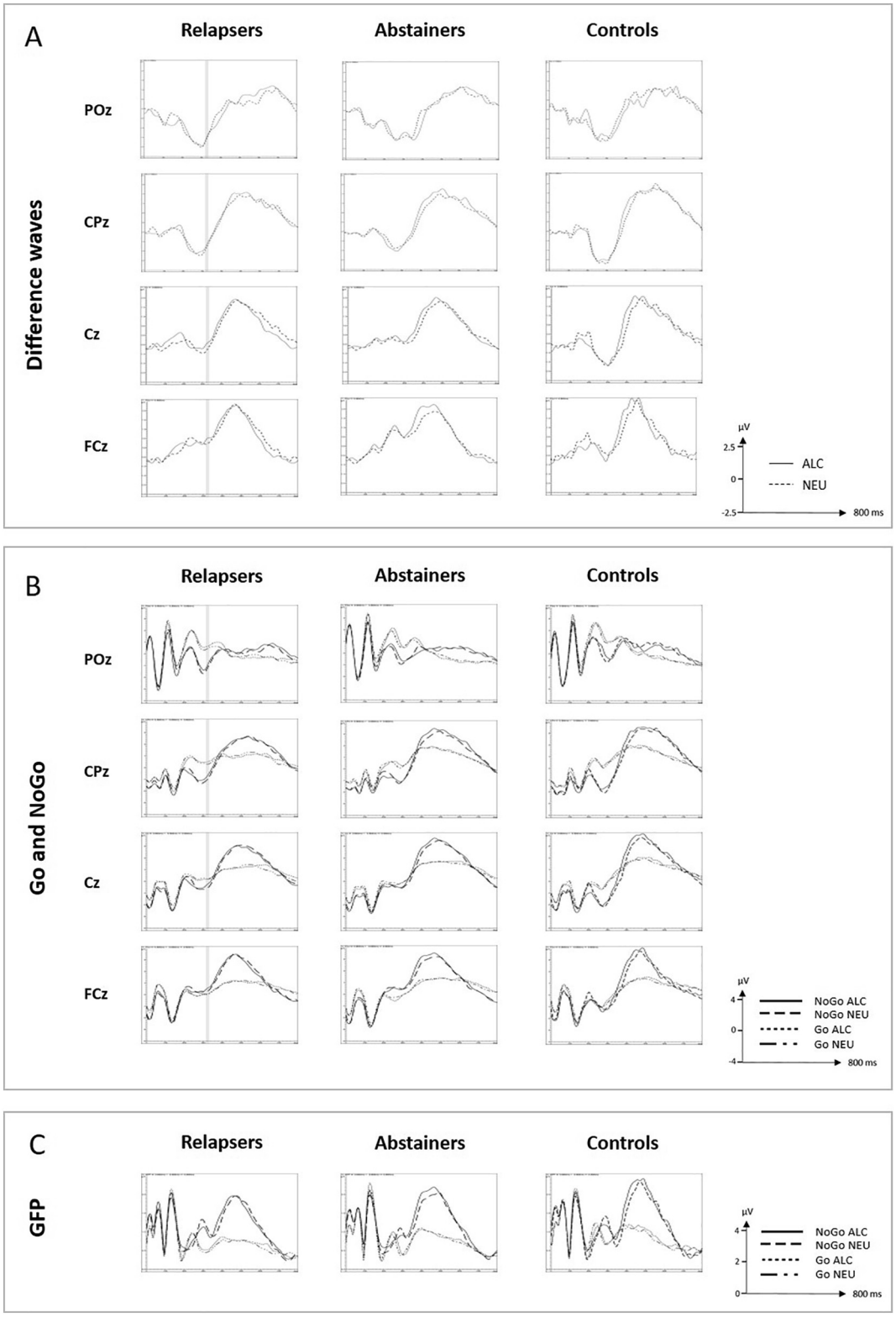

Fig. 3. Event-Related Potentials (ERPs) for alcohol-related and neutral trials shown separately for relapsers, abstainers and controls. Shaded areas in Fig. 3A and B denote the timeframe in which topographical analyses indicated that in relapsers (but not in abstainers or controls) inhibition-specific P3 activation differed between alcohol-related and neutral NoGo trials. A: Difference waves (NoGo-Go) at exemplary electrodes. B: Single channel ERPs for Go and NoGo-trials at exemplary electrodes. C: Global Field Power (GFP) curves. Abbreviations: ALC: Alcohol, NEU: Neutral, ms: Milliseconds, µV: Microvolt.

When investigating the third research question, whether the electrophysiological data during the GNG task differentiated between relapsers and abstainers, a significant three-way interaction between relapse/abstinence, response type and picture type was found in the P3 component, as hypothesized. While the topographic interaction between picture type and response type was

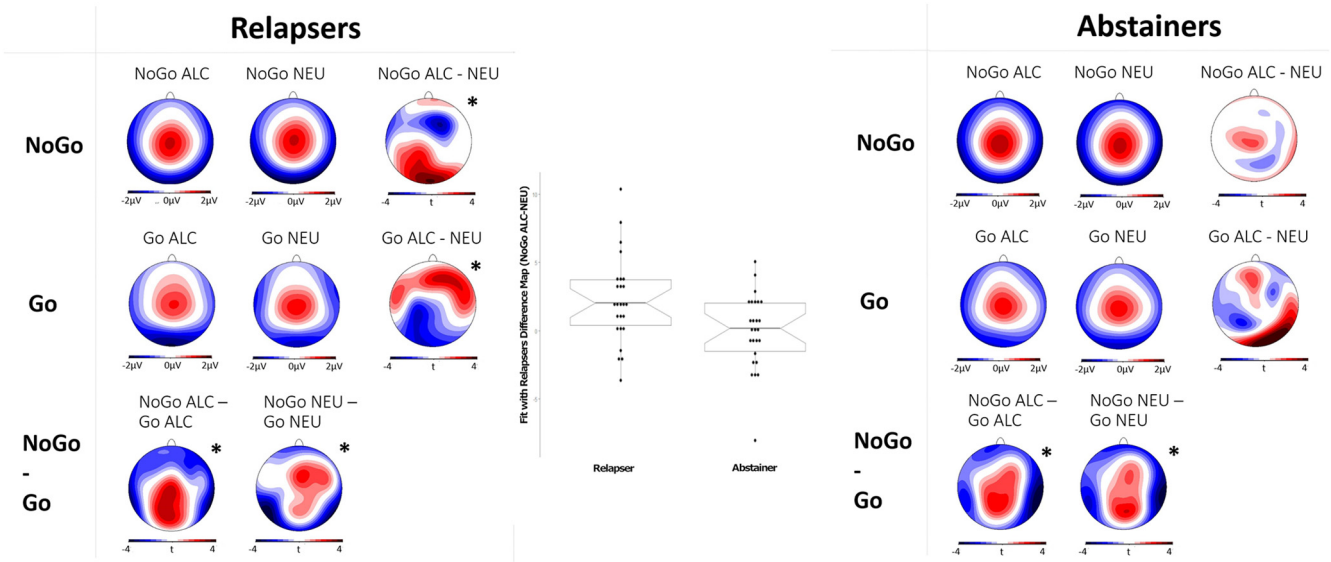

Fig. 4. Depiction of the four ERP maps averaged between 516–538 ms and difference maps of the four possible comparisons (NoGo ALC minus NoGo NEU, Go ALC minus Go NEU, NoGO ALC minus Go ALC, NoGo NEU minus Go NEU) in relapsers (left) and abstainers (right). Notes: In NoGo trials, relapsers show more negativity in right-sided frontal electrodes in alcohol compared to neutral trials, whereas in Go trials, the opposite pattern occurs. Here, in right frontal-sided electrodes, there is more positivity frontally in ALC compared to NEU trials. In abstainers, these differences are not significant, which is reflected by smaller t values and accordingly, less intense colors of the t maps. The asterisk indicates significant topographical differences in the respective comparisons. The notched boxplot in the middle shows individual quantifiers of the significant ALC-NEU difference in the NoGo trials as observed in relapsers. These individual quantifiers were obtained by computing spatially weighed means across electrodes in the individual difference maps, whereas these weights were given by the relapsers GFP-normalized mean difference map (NoGo ALC – NEU). The plot shows that this quantifier varies between individual subjects and is (as expected) higher in relapsers. Notches in the plot represent confidence interval around the median values of the individual quantifiers. Abbreviations: ALC: alcohol; NEU: neutral; μV: microvolt; t: t-values.

significant in relapsers, this was neither observed in the abstinent group of AUD patients nor in the control group. In relapsers only, the picture type had a differential effect in Go compared to NoGo trials: In NoGo trials, alcohol-related pictures evoked more right-lateralized frontal negativity than did the neutral pictures, whereas in Go trials, an opposite pattern occurred. None of these comparisons indicated significant topographical differences in abstainers. Thus, the picture type selectively influenced the P3 component of relapsers but not abstainers in a way that differed between Go and NoGo trials. Therefore, only in relapsers, inhibition-specific P3 activation, which is thought to reflect effective inhibition (Smith et al., 2008), differed between alcohol-related and neutral contexts.

In line with prior studies (Petit et al., 2014, Campanella et al., 2019a), our results suggest that inhibition-specific neurophysiological activity — as indicated by difference waves or by a three-way interaction in the P3 component — differentiates between abstainers and relapsers. The specific pattern describing this differentiation, however, varies between studies: Petit et al. (2014) revealed an increased P3 difference wave (NoGo - Go) amplitude at a frontocentral cluster of six electrodes in relapsers as compared to abstainers, but observed no differences between neutral and alcohol-related context. Another study (Campanella et al., 2019a) analyzed ERP changes in the course of a four-week detoxification program. Results indicated that abstainers showed an enhanced P3 difference wave at a cluster of four frontocentral electrodes for alcohol-related trials at the end of detoxification compared to the beginning, whereas relapsers showed no changes of alcohol-related or neutral P3 difference waves. While the results of Campanella et al. (2019a) and our results align in indicating effects involving the alcohol-related context, Petit et al. (2014) observed that the neurophysiology related to general inhibition differentiates between relapsers and abstainers. Furthermore, while (Petit et al., 2014) suggested that a larger P3 difference wave describes relapsers (when compared to abstainers), the results reported by Campanella et al. (2019a) seem to suggest that an increase in P3 difference waves over the course of detoxification, at least in an alcohol-related context, is a characteristic of abstainers. Because we did not observe an effect in signal strength (GFP), we cannot contribute to clarifying this inconsistency in one way or another. Coming from a different methodological perspective, our results tell a slightly different story: While the picture type affected the topography of relapsers, it did not impact those of abstainers and controls. Theoretically, since single-channel analyses cannot disentangle effects of signal strength and topography, such a topographic effect could also produce the aforementioned changes in single channel analyses (Campanella et al., 2019a) by changing the localization of maxima/minima which, in turn, affects the signal strength picked up at a predefined sensor position. Our topographical difference maps (Fig. 4) suggest that in relapsers, the maximum of the P3 difference wave is shifted towards posterior sensors in alcohol-related compared to neutral trials. Together with the interpretation of the NoGo-anteriorization in the P3 as a marker of effective inhibition (Fallgatter and Strik, 1999), this might indicate deficient inhibition in an alcohol-related context in relapsing patients.

Interestingly, our study aligns with the two previous studies investigating electrophysiological correlates of alcohol-specific inhibition in relation to relapse (Petit et al. 2014; Campanella et al., 2019a) of ERPs in finding effects in the P3, but not in the N2 component. The N2 seemed unaffected by relapse-status, despite the facts that a) relapsers reported higher craving than abstainers, b) our second analysis indicated that the alcohol-related N2 increased with craving and c) a post-hoc regression analysis linked craving to relapse ($\chi 2(1) = 5.74$, $p < .02$; Nagelkerke $R^2 = 0.14$). As such, our study complements prior reports proposing the P3 component as a biomarker to identify those AUD patients with an increased risk for relapse (Petit et al., 2014, Campanella et al., 2019a), even though one has to acknowledge that future studies yet have to clarify precisely which alteration (increase,

decrease or topographical alteration) is the most promising predictor. Once a reliable predictor is identified, this might support the claim that the neurophysiological examination of AUD patients could contribute to providing a more individualized treatment and, in turn, to ameliorate treatment success (Campanella et al., 2019b, Bauer, 2001, Saletu-Zyhlarz et al., 2004, Marhe et al., 2014, Petit et al., 2014).

Although the general notion is that AUD patients have attenuated inhibitory control compared to healthy controls (Petit et al., 2014, Smith et al., 2014), findings in previous studies on behavioral inhibitory control differences between AUD patients and control are mixed. Our results add to those studies that do not detect inhibitory deficits on a behavioral level, neither in reaction times, nor in accuracy and/or error rates (Karch et al., 2007, Stein et al., 2018, Fallgatter et al., 1998, Kamarajan et al., 2005a). A possible methodological explanation might concern variation in the speed of and/or stimuli in the GNG task.

Another aspect related to the GNG is important to mention. Given the fast-paced GNG task, we had to deal with the possibility of preparatory ERPs, such as contingent negative variation (CNV) as well as the offset component from a previous stimulus possibly, overlapping particularly with early ERP components, thus potentially interfering in our analyses. In order to overcome this limitation, we chose a data reduction and analysis strategy that incorporated two key steps: First, we restricted the calculation of Go ERPs to those Go trials which were preceded by a stimulus of the same type, for example Go ALC after Go ALC. Given that the same applied to NoGo trials (by definition preceded by an identical stimulus), we could, therefore, achieve a matching of the prestimulus interval in Go and NoGo trials, in order to deliberately cancel out any effects introduced by such components when subtracting go from NoGo trials. Secondly, we focused our analysis on effects incorporating such a subtraction (i.e., effects involving the factor response type, which are computed on the basis of such difference maps subtracting Go from NoGo trials). Thus, while the offset components are still present in the descriptive waveforms, our effects are not contaminated by these components.

As a potential limitation, the outcome used to separate the patient group in relapsers and abstainers was dichotomous, with relapse being defined as any alcohol consumption within the three months after treatment discharge, regardless of its amount or frequency. It cannot be ruled out that defining relapse differently, for example as a minimum amount of heavy drinking days, or using a more holistic outcome, such as trajectories, would allow to better grasp the complexity of drinking behavior change. In turn, this may have resulted in different findings (see Witkiewitz and Marlatt, 2007).

Furthermore, regarding GNG research in AUD patients, there is debate as to whether disinhibition is a cause or rather a consequence of alcohol use. Two possible and not mutually exclusive explanations are either that chronic AUD consumption leads to increased inhibitory control deficits via neurotoxic effects in the prefrontal cortex, or that young individuals with decreased inhibitory control have a higher risk of developing AUD (Jones et al., 2013). Thus, future longitudinal could shed light upon these mechanisms.

5. Summary and conclusion

In summary, we did not observe behavioral or neurophysiological differences in inhibitory control on the group level. However, we did observe the neurophysiological correlates of alcohol-specific inhibition to vary with individual craving levels as well as drinking outcome in the three months after treatment discharge: Regarding the N2 component, and in line with an earlier study (Stein et al., 2018), the topographic difference between alcohol-specific and neutral inhibition increased with craving, possibly indicating higher conflict during alcohol-specific inhibition in patients with intense craving. In the P3 component, we observed topographical differences between alcohol-specific and neutral inhibition in relapsers, which were not found in abstainers or controls. While the precise pattern of P3 effects remains to be fully clarified, our results support the notion of the NoGo-P3 being a neurophysiological marker of an altered inhibitory control processing that may facilitate relapse.

Taken together, our results extend existing reports on the neurophysiology of alcohol-specific inhibition in AUD patients. Clinically relevant, they contribute to a growing body of research indicating that inhibitory control ERPs might be useful in monitoring the relapse risk in AUD patients (Houston and Schlienz, 2018, Campanella et al., 2019b). Furthermore, the fact that it was not the group level but rather individual parameters, such as craving and drinking outcome that accounted for neurophysiological differences, indicates a considerable heterogeneity within the AUD patient sample. By incorporating ERPs in treatment planning, a larger part of this heterogeneity – which includes neurophysiology – could be captured and might contribute to a more personalized treatment.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

Agarwalla PA, Koss A, Küchenhoff J. Abstinenz nach stationärer qualifizierter Entzugsbehandlung für Alkoholabhängige. Sucht 2017;63(1):25–32.
American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Washington, DC; 2013.
Aragues M, Jurado R, Quinto R, Rubio G. Laboratory paradigms of impulsivity and alcohol dependence: a review. Eur. Addict. Res. 2011;17(2):64-71.
Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG. The Alcohol Use Disorders Identification Test. guidelines for use in primary care. Geneva: World Health. Organization 2001.
Bauer LO. Predicting relapse to alcohol and drug abuse via quantitative electroencephalography. Neuropsychopharmacology 2001;25(3):332–40.
Blanco-Ramos J, Cadaveira F, Folgueira-Ares R, Corral M, Rodríguez Holguín S. Electrophysiological correlates of an alcohol-cued go/nogo task: a dual-process approach to binge drinking in university students. Int. J. Environ. Res. Public Health 2019;16(22):4550.
Bokura H, Yamaguchi S, Kobayashi S. Electrophysiological correlates for response inhibition in a Go/NoGo task. Clin. Neurophysiol. 2001;112(12):2224–32.
Boothby LA, Doering PL. Acamprosate for the treatment of alcohol dependence. Clin. Ther. 2005;27(6):695–714.
Burren Y, Wapp M, Seitz A, Ballinari P, Moggi F. Obsessive Compulsive Drinking Scale (OCDS-G): Psychometrische Kennwerte alkoholabhängiger Patienten in der Schweiz. Sucht 2012;58(2):119–25.
Campanella S, Schroder E, Kajosch H, Hanak C, Veeser J, Amiot M, et al. Neurophysiological markers of cue reactivity and inhibition subtend a three-month period of complete alcohol abstinence. Clin. Neurophysiol. 2019a;131(2):555–65.

Campanella S, Schroder E, Kajosch H, Noel X, Kornreich C. Why cognitive event-related potentials (ERPs) should have a role in the management of alcohol disorders. Neurosci. Biobehav. Rev. 2019b;106:234–44.
Colrain IM, Sullivan EV, Ford JM, Mathalon DH, McPherson S-L, Roach BJ, et al. Frontally mediated inhibitory processing and white matter microstructure: age and alcoholism effects. Psychopharmacology (Berl) 2011;213(4):669–79.
Czapla M, Simon JJ, Friederich H-C, Herpertz SC, Zimmermann P, Loeber S. Is binge drinking in young adults associated with an alcohol-specific impairment of response inhibition?. Eur. Addict. Res. 2015;21(2):105–13.
Czapla M, Simon JJ, Richter B, Kluge M, Friederich HC, Herpertz S, et al. The impact of cognitive impairment and impulsivity on relapse of alcohol-dependent patients: implications for psychotherapeutic treatment. Addict. Biol. 2016;21 (4):873–84.
Donkers FC, van Boxtel GJ. The N2 in go/no-go tasks reflects conflict monitoring not response inhibition. Brain Cogn. 2004;56(2):165–76.
Fallgatter A, Strik W. The NoGo-anteriorization as a neurophysiological standard-index for cognitive response control. Int. J. Psychophysiol. 1999;32(3):233–8.
Fallgatter A, Wiesbeck G, Weijers H-G, Boening J, Strik W. Event-related correlates of response suppression as indicators of novelty seeking in alcoholics. Alcohol Alcohol. 1998;33(5):475–81.
Field M, Marhe R, Franken IH. The clinical relevance of attentional bias in substance use disorders. CNS spectrums 2014;19(3):225–30.
Finney JW, Moos RH, Timko C. The course of treated and untreated substance use disorders: Remission and resolution, relapse and mortality. In: McCrady BS, Epstein EE, editors. Addictions: A comprehensive guidebook. Oxford University Press; 1999. p. 30–49.
Fleming KA, Bartholow BD. Alcohol cues, approach bias, and inhibitory control: applying a dual process model of addiction to alcohol sensitivity. Psychol. Addict. Behav. 2014;28(1):85–96.
Gauggel S, Heusinger A, Forkmann T, Boecker M, Lindenmeyer J, Miles Cox W, et al. Effects of alcohol cue exposure on response inhibition in detoxified alcohol-dependent patients. Alcohol. Clin. Exp. Res. 2010;34(9):1584–9.
Géczy I, Czigler I, Balazs L. Effects of cue information on response production and inhibition measured by event-related potentials. Acta Physiol. Hung. 1999;86 (1):37–44.
Habermann M, Weusmann D, Stein M, Koenig T. A Student's Guide to Randomization Statistics for Multichannel Event-Related Potentials Using Ragu. Front. Neurosci. 2018;12:355.
Houston RJ, Schlienz NJ. Event-related potentials as biomarkers of behavior change mechanisms in substance use disorder treatment. Biol. Psychiatry Cogn. Neurosci. Neuroimaging 2018;3(1):30–40.
Jin H, Rourke SB, Patterson TL, Taylor MJ, Grant I. Predictors of relapse in long-term abstinent alcoholics. J. Stud. Alcohol 1998;59(6):640–6.
Jones A, Christiansen P, Nederkoorn C, Houben K, Field M. Fluctuating disinhibition: implications for the understanding and treatment of alcohol and other substance use disorders. Front. Psychiatry 2013;4:140.
Kamarajan C, Porjesz B, Jones K, Choi K, Chorlian D, Padmanabhapillai A, et al. Alcoholism is a disinhibitory disorder: Neurophysiological evidence from a Go/No-Go task. Biol. Psychol. 2005;.69(3):pp..
Kamarajan C, Porjesz B, Jones K, Chorlian D, Padmanabhapillai A, Rangaswamy M, et al. Spatial-anatomical mapping of NoGo-P3 in the offspring of alcoholics: evidence of cognitive and neural disinhibition as a risk for alcoholism. Clin. Neurophysiol. 2005;116(5):1049–61.
Karch S, Graz C, Jager L, Karamatskos E, Stammel A, Flatz W, et al. Influence of anxiety on electrophysiological correlates of response inhibition capacities in alcoholism. Clin. EEG Neurosci. 2007;38(2):89–95.
Koenig T, Kottlow M, Stein M, Melie-Garcia L. Ragu: a free tool for the analysis of EEG and MEG event-related scalp field data using global randomization statistics. Comput. Intell. Neurosci. 2011;2011 938925.
Koenig T, Melie-García L, Stein M, Strik W, Lehmann C. Establishing correlations of scalp field maps with other experimental variables using covariance analysis and resampling methods. Clin. Neurophysiol. 2008;119(6):1262–70.
Korucuoglu O, Gladwin TE, Wiers RW. Alcohol-induced changes in conflict monitoring and error detection as predictors of alcohol use in late adolescence. Neuropsychopharmacology 2015;40(3):614–21.
Korucuoglu O, Gladwin TE, Wiers RW. The effect of acute alcohol on motor-related EEG asymmetries during preparation of approach or avoid alcohol responses. Biol. Psychol. 2016;114:81–92.
Lannoy S, Maurage P, D'Hondt F, Billieux J, Dormal V. Executive impairments in binge drinking: evidence for a specific performance-monitoring difficulty during alcohol-related processing. Eur. Addict. Res. 2018;24(3):118–27.
Lehmann D, Skrandies W. Reference-free identification of components of checkerboard-evoked multichannel potential fields. Electroencephalogr. Clin. Neurophysiol. 1980;48(6):609–21.
Logan GD, Cowan WB, Davis KA. On the ability to inhibit simple and choice reaction time responses: a model and a method. J. Exp. Psychol. Hum. Percept. Perform. 1984;10(2):276.
Luijten M, Machielsen MW, Veltman DJ, Hester R, de Haan L, Franken IH. Systematic review of ERP and fMRI studies investigating inhibitory control and error processing in people with substance dependence and behavioural addictions. J. Psychiatry Neurosci. 2014;39(3):149–69.
Mann K, Ackermann K. Die OCDS-G: Psychometrische Kennwerte der deutschen Version der obsessive compulsive drinking scale. Sucht 2000;46(2):90–100.
Marhe R, Franken IH, Luijten M. The clinical relevance of neurocognitive measures in addiction. Front. Psychiatry 2014;4:185.
Murray MM, Michel CM, De Peralta RG, Ortigue S, Brunet D, Andino SG, et al. Rapid discrimination of visual and multisensory memories revealed by electrical neuroimaging. Neuroimage 2004;21(1):125–35.
Nederkoorn C, Baltus M, Guerrieri R, Wiers RW. Heavy drinking is associated with deficient response inhibition in women but not in men. Pharmacol. Biochem. Behav. 2009;93(3):331–6.
Noël X, Bechara A, Brevers D, Verbanck P, Campanella S. Alcoholism and the loss of willpower: A neurocognitive perspective. J. Psychophysiol. 2010;24(4):240.
Noel X, Van der Linden M, d'Acremont M, Bechara A, Dan B, Hanak C, et al. Alcohol cues increase cognitive impulsivity in individuals with alcoholism. Psychopharmacology (Berl) 2007;192(2):291–8.
Oddy BW, Barry RJ. The relationship of N2 and P3 to inhibitory processing of social drinkers in a Go/NoGo task. Int. J. Psychophysiol. 2009;72(3):323–30.
Pandey A, Kamarajan C, Tang Y, Chorlian D, Roopesh B, Manz N, et al. Neurocognitive deficits in male alcoholics: an ERP/sLORETA analysis of the N2 component in an equal probability Go/NoGo task. Biol. Psychol. 2012;89 (1):170–82.
Pascual-Marqui RD. Standardized low-resolution brain electromagnetic tomography (sLORETA): technical details. Methods Find. Exp. Clin. Pharmacol. 2002;24(Suppl D):5–12.
Petit G, Cimochowska A, Kornreich C, Hanak C, Verbanck P, Campanella S. Neurophysiological correlates of response inhibition predict relapse in detoxified alcoholic patients: some preliminary evidence from event-related potentials. Neuropsychiatr. Dis. Treat. 2014;10:1025–37.
Petit G, Kornreich C, Noël X, Verbanck P, Campanella S. Alcohol-related context modulates performance of social drinkers in a visual Go/No-Go task: a preliminary assessment of event-related potentials. PLoS One 2012;7(5) e37466.
Prince M, Patel V, Saxena S, Maj M, Maselko J, Phillips MR, et al. No health without mental health. Lancet 2007;370(9590):859–77.
Rehm J, Mathers C, Popova S, Thavorncharoensap M, Teerawattananon Y, Patra J. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. Lancet 2009;373(9682):2223–33.
Robinson TE, Berridge KC. Incentive-sensitization and addiction. Addiction 2001;96 (1):103–14.
Rohde KB, Caspar F, Koenig T, Pascual-Leone A, Stein M. Neurophysiological traces of interpersonal pain: How emotional autobiographical memories affect event-related potentials. Emotion 2018;18(2):290.
Saletu-Zyhlarz GM, Arnold O, Anderer P, Oberndorfer S, Walter H, Lesch OM, et al. Differences in brain function between relapsing and abstaining alcohol-dependent patients, evaluated by EEG mapping. Alcohol Alcohol. 2004;39 (3):233–40.
Shelton J, Kumar GP. Comparison between auditory and visual simple reaction times. Neurosci. Med. 2010;1(1):30–2.
Smith Mattick, Jamadar Iredale. Deficits in behavioural inhibition in substance abuse and addiction: a meta-analysis. Drug Alcohol Depend. 2014;145:1–33.
Smith JL, Johnstone SJ, Barry RJ. Movement-related potentials in the Go/NoGo task: the P3 reflects both cognitive and motor inhibition. Clin. Neurophysiol. 2008;119(3):704–14.
Stein M, Fey W, Koenig T, Oehy J, Moggi F. Context-Specific Inhibition is Related to Craving in Alcohol Use Disorders: A Dangerous Imbalance. Alcohol. Clin. Exp. Res. 2018;42(1):69–80.
Sudhinaraset M, Wigglesworth C, Takeuchi DT. Social and cultural contexts of alcohol use: Influences in a social–ecological framework. Alcohol Res. Health 2016;38(1):35–45.
Walter M, Dürsteler K, Petitjean S, Wiesbeck G, Euler S, Sollberger D, et al. Psychosocial Treatment of Addictive Disorders–An Overview of Psychotherapeutic Options and their Efficacy. Fortschr. Neurol. Psychiatr. 2015;83(4):201–10.
Weisner C, Matzger H, Kaskutas LA. How important is treatment? One-year outcomes of treated and untreated alcohol-dependent individuals. Addiction 2003;98(7):901–11.
Wiers RW, Bartholow BD, van den Wildenberg E, Thush C, Engels RC, Sher KJ, et al. Automatic and controlled processes and the development of addictive behaviors in adolescents: a review and a model. Pharmacol. Biochem. Behav. 2007;86(2):263–83.
Witkiewitz K, Marlatt GA. Modeling the complexity of post-treatment drinking: It's a rocky road to relapse. Clin. Psychol. Rev. 2007;27(6):724–38.
Wolz I, Sauvaget A, Granero R, Mestre-Bach G, Baño M, Martín-Romera V, et al. Subjective craving and event-related brain response to olfactory and visual chocolate cues in binge-eating and healthy individuals. Sci. Rep. 2017;7 (1):1–10.