Context-Specific Inhibition is Related to Craving in Alcohol Use Disorders: A Dangerous Imbalance

Maria Stein, Werner Fey, Thomas Koenig, Jacqueline Oehy, and Franz Moggi

Background: Most contemporary neuroscientific models of alcohol use disorders (AUD) incorporate an imbalance between enhanced cue reactivity, which results in a strong urge to consume, and the impaired inhibitory control of that urge. While these phenomena have been frequently investigated separately, studies involving both aspects and thus precisely investigating the postulated imbalance are rare. In this study, inhibition was investigated in an addiction-specific context and individual craving levels were also examined.

Methods: This study compared inhibition in alcohol-related and neutral contexts in patients with AUD and healthy controls, while also taking into account the individual amount of craving. All subjects performed a Go/NoGo task involving neutral and alcohol-related NoGo trials, while their brain activity was recorded using multichannel electroencephalography. The map strength and topography of the N2 and P3 components of the NoGo event-related potentials were compared between groups and contexts using whole-scalp randomization-based methods. The effects of interest were further investigated with sLORETA source analysis.

Results: For the N2 component, the context by craving interaction was strong for map strength and map topography. The source analysis indicated that in subjects with high craving, alcohol-related context led to enhanced and prolonged activation in the posterior cingulate and premotor cortical areas. This interaction was specific for craving, but not for diagnostic classification. The amplitude of the P3 component was reduced in subjects with AUD, which replicated previous findings.

Conclusions: In subjects with strong craving, the conflict reflected in the NoGo-N2 was enhanced in the alcohol-related context. Such enhanced conflict probably makes the successful inhibition of the urge to drink in high-risk situations even more difficult for this subgroup of patients and should therefore be addressed in individualized treatment planning.

Key Words: Alcohol Use Disorders, Craving, Inhibition, Event-Related Potentials, N2.

MOST CONTEMPORARY NEUROSCIENTIFIC models of addiction and relapse in substance use disorders (SUD) focus on an important imbalance. On one side, enhanced cue reactivity results in a strong urge to consume, which is also experienced as craving, and, on the other side, the impaired control system struggles, often in vain, to inhibit that urge (Volkow and Baler, 2014; Wiers et al., 2013). Alterations in both phenomena have been demonstrated in patients with alcohol use disorders (AUD) in a variety of studies. Enhanced cue reactivity has been demonstrated in patients with AUD and other SUD using behavioral paradigms and neurophysiological measures (Herrman et al., 2000; Jasinska et al., 2014; Schacht et al., 2013). Similarly, many researchers have reported impaired inhibitory control at the behavioral level or brain activation differences during inhibition when patients with AUD and SUD were compared to control subjects (Fallgatter et al., 1998; Kamarajan et al., 2005a; Luijten et al., 2014; Smith et al., 2014). Even more important than the findings demonstrating impaired inhibition in general are assessments of the inhibition of alcohol-related cues. Precisely this context-specific inhibition, the deficits of which have been postulated by several addiction models, is critical for patients striving to stay abstinent in the presence of alcohol-related triggers.

Behavioral studies of inhibition in alcohol-related contexts have yielded inconsistent results. Some authors have reported increased inhibitory deficits in that setting (Noel et al., 2007; Weafer and Fillmore, 2012), while others have not (Houben et al., 2012; Nederkoorn et al., 2009). Neuroscientific studies that specifically investigate inhibition in alcohol-related contexts are still scarce and have, with very few exceptions (Petit et al., 2014), mainly been conducted with social drinkers (Korucuoglu et al., 2015; Kreusch et al., 2014; Petit et al., 2012). Studies focusing on the postulated imbalance in a patient group and examining the neurophysiological correlates of context-specific inhibition in AUD are needed.

In neuroscientific research, Go/NoGo tasks are commonly used to assess inhibitory control. In these tasks, a continuous

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series of stimuli that require a response (Go stimuli) is interrupted by the presentation of stimuli requiring inhibition of this prepotent response (NoGo stimuli). Typically, the Go/NoGo ratio in these experiments is quite high in order to establish a strong tendency to respond (Hester et al., 2004; but see also Pandey et al., 2012). When event-related potentials (ERPs) are recorded during these tasks, 2 ERP components are repeatedly associated with inhibitory control. The first is the N2 component, which is topographically characterized by a frontocentral minimum in NoGo trials (NoGo-N2) and peaks between 200 and 400 ms after stimulus onset. The N2 component is thought to reflect the detection of response conflict (or the recognition of the need for inhibition) and higher processing demands (Donkers and van Boxtel, 2004; Nieuwenhuis et al., 2003; Zhang and Lu, 2012). During NoGo trials, the N2 component is followed by a P3 component (NoGo-P3), which is characterized by a frontocentral maximum that peaks between 300 and 700 ms with a topographical pattern that is typically more anteriorly distributed than it is in Go trials. This NoGo-P3 component has been suggested as a marker of effective inhibition (Fallgatter et al., 1998; Smith et al., 2008; Zhang and Lu, 2012).

In electrophysiological research using Go/NoGo tasks in patients with AUD, changes in the amplitude and/or latency of the NoGo-N2 and, more often, the NoGo-P3 are among the most prevalent findings. One study reported low amplitudes and differences in neural generator configuration for the NoGo-N2 (Pandey et al., 2012) in patients with AUD compared to healthy controls, while another study did not observe any changes in N2 (Petit et al., 2014). Earlier studies using oddball paradigms have reported N2 latency alterations in patients with AUD (Porjesz et al., 1987) and suggested that N2 latencies might predict relapse in abstinent patients with AUD (Glenn et al., 1993).

A decreased amplitude of the NoGo-P3 has been found in patients with AUD (Colrain et al., 2011; Kamarajan et al., 2005a), heavy drinkers (Oddy and Barry, 2009), and relatives of patients with AUD (Kamarajan et al., 2005b) compared to healthy controls. However, Petit and colleagues (2014) have found a larger NoGo-P3 and an enhanced Go/NoGo difference wave (P3d) in patients with AUD. Interestingly, the amplitude of the P3d wave discriminated relapsers from abstainers (Petit et al., 2014). Furthermore, differences in P3 scalp topography (Fallgatter et al., 1998) and underlying generators (Kamarajan et al., 2005a) have been reported in patients with AUD.

As stated above, inhibitory control deficits in patients with AUD are especially significant in the context of alcohol-related cues and when these patients have to suppress a strong urge to consume alcohol. Neurophysiological research focusing on the postulated imbalance between highly salient alcohol-related cues and context-specific inhibition in Go/NoGo tasks is rare. Of special interest in this respect is the study by Petit and colleagues (2014) that compared neutral and alcohol-related NoGo contexts and reported no interaction between group and context. The present study therefore not only focused on group differences but also examined the influence of craving on context-specific inhibitory deficits. Based on earlier research, statistical analyses considered only the NoGo-N2 and NoGo-P3 components. These components were analyzed with randomization-based statistical methods that take into account the entire scalp field, are reference independent (see also Koenig et al. [2008, 2011] and the Materials and Methods section), overcome the limitations introduced by a priori selections of electrodes and time periods, and allow for the separation of effects explained by source configuration changes from the effects due to source strength changes. We assumed that inhibition in alcohol-related contexts (alcohol-related NoGos) evokes stronger conflict than inhibition in neutral contexts (neutral NoGos) in patients with AUD. Because this conflict is thought to arise between the enhanced saliency attribution and approach tendency on one side and the required inhibitory reaction on the other side, we further assumed that the conflict is related to the amount of craving or drug-use compulsions that a person experiences. Because the NoGo-N2 is thought to reflect response conflict, we thus hypothesized that patients with AUD display enhanced NoGo-N2s in alcohol-related context and that this effect is related to the levels of subjective craving.

MATERIALS AND METHODS

Participants

The patients were recruited during inpatient treatment for AUD at the University Hospital of Psychiatry and Psychotherapy in Bern. All patients were diagnosed with alcohol dependence according to the 10th revision of the International Statistical Classification of Diseases (ICD-10; WHO, 1993) and had a history of multiple years of alcohol problems. The patients were detoxified and were currently abstinent for a minimum of 8 days (mean: 28 days, range: 8 to 46 days) at the time of the study. Fifteen patients and 15 healthy controls without risky drinking habits were included in the study (see Table 1 and Supporting Information). A power analysis with conservative assumptions indicated that this sample size resulted in a power of 0.7 for the detection of interaction effects. An alcohol level of 0.0 ‰ on a breath test (Lion Alcolmeter SD-400; Lion Laboratories Limited, Barry, UK) was mandatory.

Table 1. Descriptives and Group Comparisons of the Patients and Controls

	Patients *M* (±SD)	Controls *M* (±SD)	*t*	df	*p*
Age	46.2 (±9.87)	43.4 (±13.35)	0.65	28	0.52
Education	13.9 (±1.7)	14.8 (±2.4)	2.46	28	0.02*
OCDS-O	15.4 (±10.05)	3.0 (±3.0)	4.58	28	<0.001*
OCDS-T	6.7 (±4.69)	0.6 (±1.35)	4.82	28	<0.001*
OCDS-C	8.7 (±5.90)	2.4 (±1.84)	3.97	28	0.001*
			χ^2	df	*p*
Gender	12 m; 3 f	9 m; 6 f	1.43	1	0.23

M, mean; SD, standard deviation; OCDS-O, Obsessive Compulsive Drinking Scale-overall score; OCDS-T, Obsessive Compulsive Drinking Scale-thoughts (i.e., cognitive subscale); OCDS-C, Obsessive Compulsive Drinking Scale-compulsions (i.e., behavioral subscale); m, male; f, female.
*Indicates significant results ($p < 0.05$).
Age and education are indicated in years.

Procedure

After the alcohol breath test, practice Go/NoGo task, and completion of the questionnaires, all participants completed the Go/NoGo task, while electroencephalography (EEG) was measured. Before and after the Go/NoGo task, momentary levels of alcohol craving were assessed with a 10-point scale. All patients provided informed consent prior to their participation in the study, and the study protocol was approved by the regional ethics committee. Please see the Supporting Information for more details on the procedure.

Questionnaires

All subjects completed the German version of the Obsessive Compulsive Drinking Scale (OCDS; Mann and Ackermann, 2000), which yields an overall score and subscales describing the cognitive and behavioral components of craving. The patients were asked to complete the OCDS about the week before their admission to the hospital. Assuming that the behavioral component of craving is most relevant in a motor inhibition paradigm, the behavioral subscale (OCDS-compulsions [OCDS-C]) was used as a predictor in the ERP analyses.

Three additional questionnaires were given to the control group to exclude controls with psychopathological symptoms and problematic drinking habits. The Hamilton Depression Rating Scale (Hamilton, 1960; cutoff value: 13) and global severity index (cutoff value: 63) of the Brief Symptom Inventory (German version; Franke, 2000) were used to monitor and eventually exclude controls with psychopathological symptoms. A score over 8 on the AUD identification test (Babor et al., 1992) was used to exclude controls with potentially problematic drinking behavior.

Go/NoGo Task

The Go/NoGo task was constructed to assess response inhibition in alcohol-related and neutral contexts. Stimulus material (60 alcohol-related and 60 neutral pictures) was drawn from a large database of pictures characterized for their alcohol-relatedness, valence, craving, arousal, luminance, colors, and visual complexity (Fey et al., 2017). The participants were instructed to press a button as soon as a picture appeared on the screen (Go trials) in all cases except when the stimulus was repeated (NoGo trials). Each stimulus was presented 8 times as a Go stimulus and once as a NoGo stimulus in a pseudorandomized order while controlling for position and sequential effects as well as demanding a minimum of more than 1 Go trial between 2 NoGo trials. Thus, the experiment included 480 neutral Go trials, 480 alcohol-related Go trials, 60 neutral NoGo trials, and 60 alcohol-related NoGo trials. Each picture was displayed for 900 ms (Fig. 1), with an interstimulus interval that varied between 100 and 500 ms. After half of the stimuli, the participants relaxed during a 2-minute break. The task administration and behavioral response recording were performed with E-Prime v1.1 software (PST, Sharpsburg, PA). See the Supporting Information for more details on the task and stimulus material.

Statistical Analyses of the Reaction Times and Error Rates

The reaction times (RTs) in the Go trials, RTs of the errors of commission (EOC) in the NoGo trials, and percentage of EOCs in the NoGo trials were analyzed parametrically (Kolmogorov–Smirnov test, $p > 0.05$) using a repeated-measures analysis of variance (ANOVA) with the factors picture type (alcohol-related, neutral) and group (patients, controls). Because the percentages of omissions during the Go trials were not normally distributed (Kolmogorov–Smirnov test, $p < 0.001$), Mann–Whitney *U*-tests of independent samples were used to test the between-group comparisons, while the within-group differences were analyzed with Wilcoxon signed-rank tests.

Electrophysiologic Data

EEG Recording, Preprocessing, and ERP Computation. Continuous EEG recordings were made with a digital EEG system (Neurofax EEG-1100G; Nihon Kohden Corporation, Tokyo, Japan) from scalp electrodes at 72 positions of the extended 10/10 system (impedances ≤20 kΩ; band-pass filter, 0.016 to 120 Hz; sampling rate, 500 Hz; online reference, average of C3 and C4). Two electrodes below the eyes monitored eye movement artifacts.

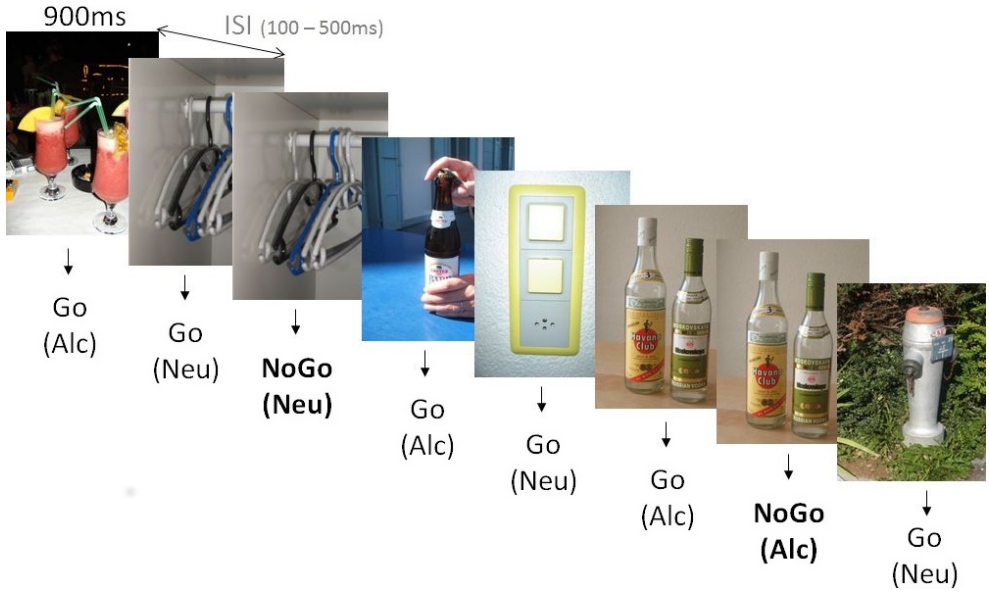

Fig. 1. Go/NoGo task incorporating neutral as well as alcohol-related pictures. Participants were instructed to press a button whenever a new stimulus appeared on screen (Go trials) and inhibit this response when a specific stimulus was repeated (NoGo trials). The ISI was randomly jittered between 100 and 500 ms. Neu, neutral; Alc, alcohol-related; ISI, interstimulus interval.

BrainVision Analyzer (Brain Products GmbH, Gilching, Germany) was used offline for preprocessing and ERP computation. Eye movement artifacts were removed with an independent component analysis (ICA) with a plug-in incorporating the ICA algorithm corresponding to EEGLAB (sccn.ucsd.edu/eeglab/index.php). The data at artifact electrodes were interpolated, the remaining artifacts were rejected, and data were filtered (band-pass filter IIR [24 dB/oct]: 0.5 to 18 Hz; notch filter: 50 Hz) and re-referenced to average reference. Then, the individual ERPs for each picture type (alcohol-related, neutral) and response type (Go, NoGo) were computed by averaging segments from 0 to 1,000 ms after stimulus onset. Thereby, the following 4 ERPs were obtained per participant: alcohol-related NoGo (alcNoGo), neutral NoGo (neuNoGo), alcohol-related Go (alcGo), and neutral Go (neuGo). During this procedure, only artifact-free segments with correct behavioral responses were included in the ERP computations. Because NoGo tasks elicit preparatory activity, we opted against using a baseline correction to avoid deliberate introduction of prestimulus activation to the stimulus processing epoch. A minimum of 20 correct and artifact-free segments per ERP was required from each participant. The mean number of correct and artifact-free segments per ERP was 381 (range: 192 to 453) for Go-ERPs and 37 (range: 20 to 53) for NoGo-ERPs.

Statistical ERP Analyses. Because this study concentrated on context-specific effects in the neurophysiological correlates of inhibition, statistical analyses focused on alcohol-related and neutral NoGo-ERPs. Go-ERPs were only included in the analyses to test whether an observed effect was linked to the picture type per se or was specific to the NoGo trials. We chose this analysis strategy instead of analyzing difference waves (NoGo minus Go) to directly focus on the differences between the 2 NoGo conditions, which allowed us to better concentrate on the focus of the study: inhibition in alcohol-related versus neutral contexts.

Microstate Analysis. The topographic distribution of the EEG scalp fields does not change randomly over time. It can be efficiently segmented into epochs of quasi-stable topography (microstates) that represent distinct steps in the stimulus processing and correspond to activation of a specific underlying generator network (Koenig et al., 2014; Lehmann and Skrandies, 1980). Microstate analyses take into account the entire scalp field and allow for data-driven and reference-independent segmentation of the continuous ERP signals into time periods with quasi-stable topographies. This approach allows ERP components to be defined without a priori assumptions of specific time frames and without restricting the analysis to a set of predefined electrodes. Here, microstate analyses were used to define the time windows of the NoGo-N2 and NoGo-P3 ERP components for subsequent analyses.

The microstate analyses were performed with Ragu software (Koenig et al., 2011). First, a modified *k*-means clustering algorithm was applied to the alcohol-related and neutral NoGo-ERPs of the patients and controls. The optimal number of microstates was defined with a cross-validation procedure (Koenig et al., 2014; please see the Supporting Information), and these microstate maps were assigned to the NoGo-ERPs.

Analyses of ERP Map Topography and Map Strength. To statistically test for the existence of differences in the generators without introducing a priori models, such as regions of interest or particular implementations of inverse solutions, we used whole-scalp statistics to examine global differences in map topography and map strength as implemented in Ragu software. Using global quantifiers of map differences also avoids problems related to multiple testing across sensors or voxels. The influence of the within-factor NoGo type (alcohol-related, neutral), categorical between-factor group (patients, controls), and continuous between-factor craving (OCDS-C score) on map topography and map strength was analyzed:

A topographic analysis of covariance (TANCOVA) establishes scalp field topographies that vary linearly with a continuous external predictor (e.g., the OCDS values) and tests these correlations for significance using bootstrapping and randomization statistics (Koenig et al., 2008). TANCOVAs have been applied before to investigate associations between electric scalp fields and external variables (e.g., Kottlow et al., 2015; Stein et al., 2013). In this study, a TANCOVA was used to investigate the association between craving (operationalized by the compulsion subscale of the OCDS) and the NoGo-N2 and NoGo-P3 components in the ERPs.

For the categorical factors (group, NoGo type, and picture type), topographic analyses of variance (TANOVAs) yield scalp topographies that systematically differ between the factor levels and use bootstrapping and randomization statistics to test the size of these topographical differences in significance (Koenig et al., 2011; Stein et al., 2006). In the Ragu software, TANOVAs and TANCOVAs can be combined to study the interaction of categorical and continuous independent variables (Koenig et al., 2011). To assess map strength, global field power (GFP; Lehmann and Skrandies, 1980) was calculated, and the differences in map strength were tested for significance using the Ragu software in an equivalent way.

The first Ragu analysis with craving (OCDS-C values) and NoGo type (alcNoGo, neuNoGo) as the between and within factors, respectively, examined whether the amount of craving interacted with the context in which inhibition was required. The second Ragu analysis, which included the factors group (patients, controls) and NoGo type (alcNoGo, neuNoGo), was designed to assess the interaction between diagnostic category and inhibitory context. Both Ragu analyses were performed twice: first to assess the differences in topography (with GFP-normalized data) and then to investigate the differences in map strength (GFP, with nonnormalized data). As done in earlier studies, Ragu analyses were computed for every time point in the N2 and P3 microstates, and a duration criterion (>25 ms) was applied to control for multiple comparisons. Significant effects of interest (i.e., interactions) were examined further with source localization. Furthermore, nonparametric correlations (Spearman-Rho) were calculated using SPSS software (IBM Corporation, Armonk, NY) to illustrate the effects of interest.

Source Analysis. Significant interactions (NoGo type × OCDS) were analyzed with standardized low-resolution brain electromagnetic tomography analysis (sLORETA) source analysis (Pascual-Marqui, 2002). Therefore, log-transformed nonnormalized (for GFP effects) or normalized (for topographic effects) current density reconstruction (CDR) values were averaged across the significant time span and subjected to voxel-wise correlational analyses which examined the association of the paired contrast (alcNoGo minus neuNoGo) and external variable (OCDS-C). Thresholds corresponding to the alpha level of 5% (2-tailed, corrected for multiple comparisons) were determined by randomization-based statistical nonparametric mapping.

RESULTS

Descriptive and Behavioral Data

Age and gender did not differ significantly between the groups, but the patients showed higher craving values as indicated by all 3 OCDS scales (Table 1) and had fewer years of education.

An ANOVA of the RT during the Go trials yielded a main effect of picture type and a significant picture type by group interaction (Table 2*A*). Post hoc *t*-tests indicated that the RT was significantly slower in the patient group during

alcohol-related Go trials compared with that during neutral Go trials, while this difference was not significant in the control group (Table 3). An ANOVA of the RT of the EOC during NoGo trials yielded no significant results (Table 2*B*). No significant differences in the error rates between the groups or contexts were observed for EOCs during NoGo trials or omissions during Go trials (Tables 2*C* and 4).

ERP Data

As mentioned before, the statistical analyses focused on the alcohol-related and neutral NoGo-ERPs (alcNoGo, neuNoGo) from both groups (Fig. 2).

Microstate Analysis

The microstate analysis indicated that an optimal number of 9 microstate maps explained 74% of the variance in the NoGo-ERPs. Figure 3 shows the occurrence of the relevant microstate maps (representing the NoGo-N2 and NoGo-P3 components) in the alcohol-related and neutral NoGo-ERPs. Based on the time of occurrence and topographic distribution, the NoGo-N2 component was identified in the pink microstate. The NoGo-P3 complex was partitioned into 3 microstates, which are depicted in yellow and light and dark green in Fig. 3, but the yellow microstate captured the peak of the component in all 4 ERPs. Therefore, this microstate was referred to as the NoGo-P3 microstate. The time window for subsequent NoGo-N2 and NoGo-P3 analyses of map strength and topography was defined according to the minimal onset and maximal offset times of the respective microstates in the 4 NoGo-ERPs and set from 202 to 334 ms (NoGo-N2) and from 358 to 570 ms (NoGo-P3).

Table 2. Results of the Analysis of Variance of (A) RT and (B, C) EOC

(A)	RT during Go trials		
	df	*F*	*p*
Group	1	2.3	0.14
Pic-type	1	14.5	0.001*
Group × Pic-type	1	5.2	0.03*
(B)	RT of EOC (NoGo trials)		
	df	*F*	*p*
Group	1	0.69	0.41
Pic-type	1	2.62	0.12
Group × Pic-type	1	0.38	0.54
(C)	% EOC (NoGo trials)		
	df	*F*	*p*
Group	1	0.07	0.80
Pic-type	1	2.32	0.14
Group × Pic-type	1	0.87	0.14

RT, reaction time; EOC, errors of commission.
*Indicates significant results ($p < 0.05$).

Table 3. RT: Means and Post Hoc *t*-Test Results

	RT			
	Mean ± SD		Post hoc *t*-test	
	alcGo	neuGo	$t_{df = 14}$	*p*
Patients	468.03 ± 68.52	456.81 ± 68.49	3.28	0.005*
Controls	428.05 ± 61.25	425.25 ± 60.12	2.05	0.06

SD, standard deviation; alcGo, alcohol-related Go trials, neuGo, neutral Go trials; RT, reaction time.
*Indicates significant results ($p < 0.05$).

Table 4. Error Rates: (A) Means of the Percentage of Errors of Commission (EOC) During NoGo Trials. (B) Mean Fractions of Omissions and Their Statistical Comparisons During Go Trials

(A)	% EOC (NoGo trials)	
	Mean ± SD	
	alcNoGo	neuNoGo
Patients	22.3 ± 10.9	26.5 ± 12.8
Controls	22.9 ± 10.5	23.9 ± 12.1

(B)	% Omissions (Go trials)			
	Mean ± SD		Within-group comparison	
	alcGo	neuGo	*Z*	*p*
Patients	3.6 ± 6.3	3.6 ± 6.5	−0.1	0.93
Controls	0.7 ± 0.6	0.7 ± 0.9	−0.71	0.49
Between-group comparison:				
Z	1.63	−1.51		
p	0.1	0.1		

SD, standard deviation; alcGo, alcohol-related Go trials; neuGo, neutral Go trials; alcNoGo, alcohol-related NoGo trials; neuNoGo, neutral NoGo trials.

Analyses of the ERP Map Topography and Map Strength

Ragu analyses were performed on the time windows defined by the NoGo-N2 and NoGo-P3 microstates.

Analyses Using Craving (OCDS-C) as a Between-Subjects Factor

The Ragu analysis using the OCDS-C subscale as the between-subjects factor and NoGo type (alcNoGo, neuNoGo) as the within-subjects factor yielded the following effects.

NoGo-N2

Effects on Map Strength. A significant OCDS-C by NoGo-type interaction between 274 and 318 ms (significant time interval: 46 ms) occurred because, with increasing OCDS-C-values, GFP in the N2 in the alcNoGo trials increased, while GFP in the N2 in the neuNoGo trials decreased. To illustrate this effect, the differences in GFP between the alcohol-related and neutral NoGo trials (alcNoGo minus neuNoGo) were plotted against the OCDS-C

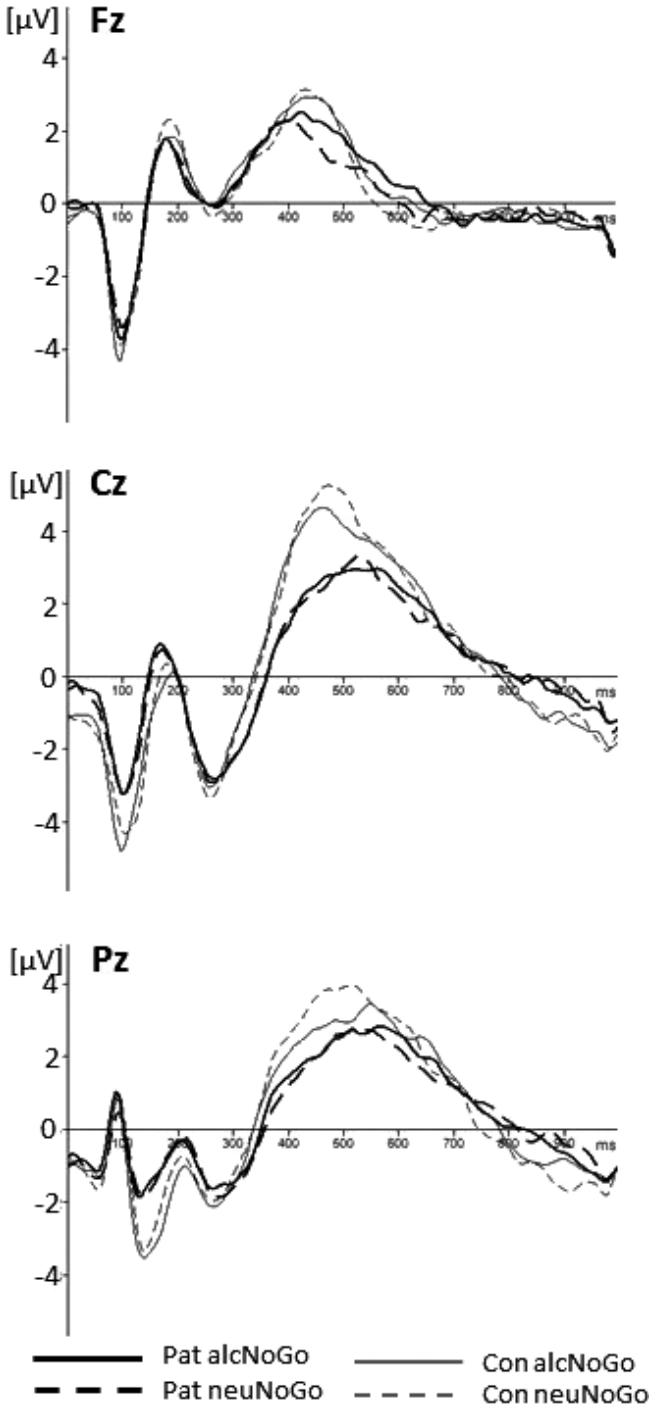

Fig. 2. Alcohol-related and neutral NoGo event-related potentials of patients and controls at Fz, Cz, and Pz. Pat, patients; Con, controls; alcNoGO, alcohol-related NoGo; neuNoGo, neutral NoGo.

values (Fig. 4*A*). The correlation between these 2 variables was significant ($p = 0.039$, $r = 0.38$). While the effect was obtained using data from all subjects (patients and controls), it was replicated and became stronger when the analyses were restricted to patients, both in the Ragu analyses (all p-values < 0.05 between 264 and 318 ms) and correlational analyses in SPSS ($p = 0.01$, $r = 0.64$). To determine whether this effect could be attributed to context-specific inhibition or whether it had to be interpreted as a general picture-type effect, Go trials were included in the analysis, and a Go Type (Go, NoGo) × Picture Type (alcohol, neutral) × OCDS-C Analysis was computed. This yielded a significant 3-way interaction (Go Type × Pic-type Picture Type × OCDS-C) between 298 and 306 ms. In this time frame, GFP during the NoGo trials, but not during the Go trials, differed between the alcohol-related and neutral contexts, and this difference increased with increasing OCDS-C values. Thus, the effect results from context-specific inhibition. Neural generators of this effect were investigated with sLORETA source analysis.

Topographic Effects. A significant OCDS-C by NoGO-type interaction was found between 304 and 330 ms (significant time interval: 28 ms). During this time period, the topography of the neutral NoGo-ERP of the subjects with high OCDS values comprised a right-lateralized maximum over parieto-occipital electrodes, while the topography of the alcohol-related NoGo-ERPs of the subjects with high OCDS values comprised a bilateral (or even left-lateralized) maximum over parieto-occipital electrodes. To illustrate this effect, the mean difference map between these 2 topographies was calculated (Fig. 4*B*). Furthermore, individual difference maps (alcNoGo minus neuNoGo) were computed for each subject. These individual difference maps were then projected onto the mean difference map to quantify the amount of variance that was explained by the mean difference (topographic fitting). The mean strength of this fit within the significant time period (304 to 330 ms) therefore reflected the strength of the topographical difference described above between the alcNoGo-ERPs and neuNoGo-ERPs in every subject. The correlation (Spearman's rho) between this fit with the difference map and OCDS-C values (Fig. 4*B*) was significant ($p = 0.006$, $r = 0.49$). Even if this effect was obtained using data from the whole group, it was mainly driven by the patients, and it was replicated when the analyses were restricted to patients in the Ragu analyses (all p-values < 0.05 from 308 to 320 ms) as well as the correlational analysis ($p = 0.002$, $r = 0.72$).

To investigate whether this effect was restricted to NoGo trials or represented a more general picture-type effect and was also present in Go trials, the analysis was repeated in Go trials, in which the interaction was not replicated. In the 3-factorial Ragu analysis with the factors Go Type (Go, NoGo), Picture Type (alcohol, neutral), and OCDS-C, the 3-way interaction (Pic-type × Go Type × OCDS-C) only yielded a trend for significance. We therefore concluded that this was a NoGo-driven effect that was not strong enough to produce a 3-way interaction.

NoGo-P3

Effects on Map Strength (GFP). No significant effects were observed on the NoGo-P3.

Topographic Effects. No main effect of OCDS and no significant interaction were found. There were main effects of

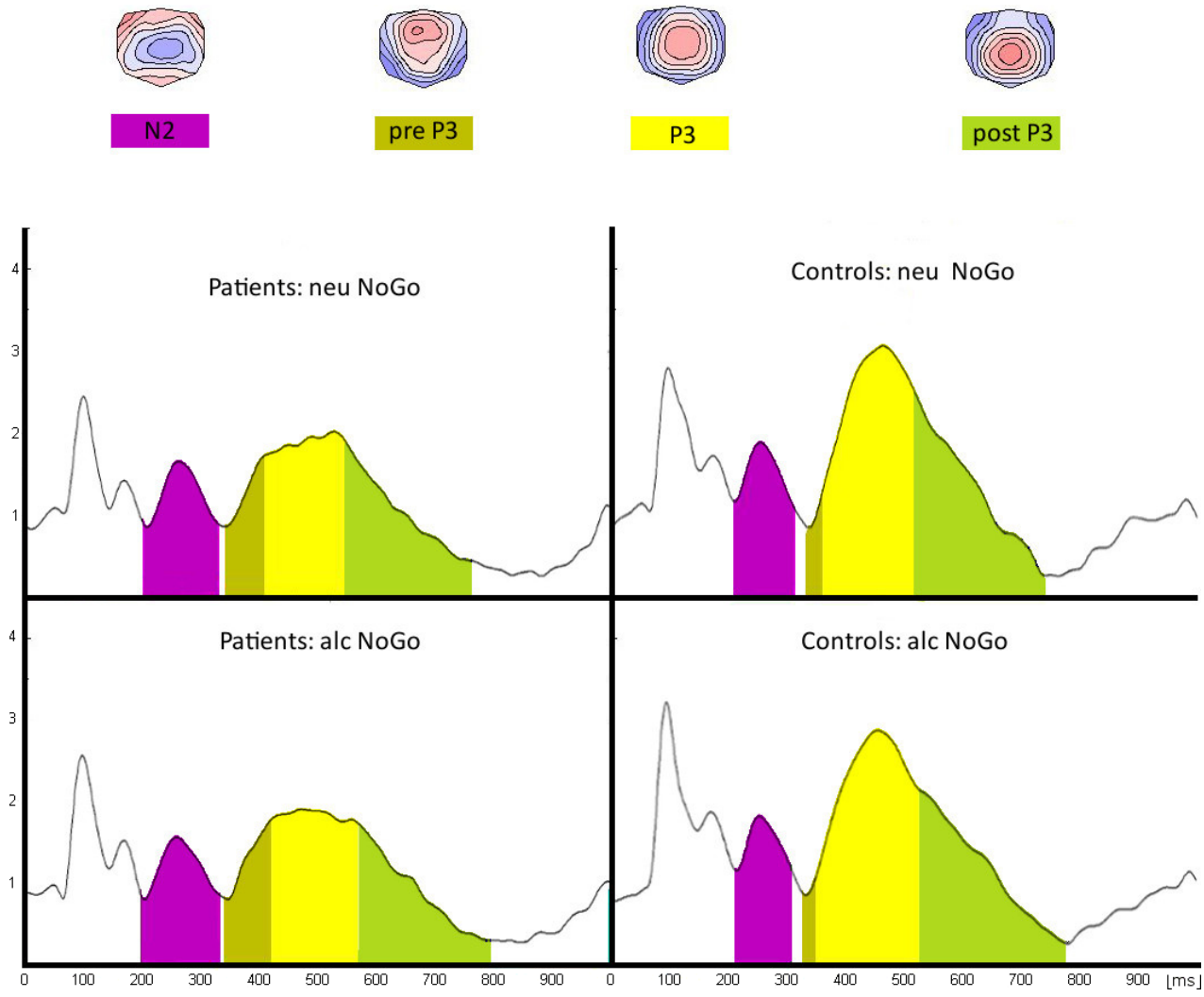

Fig. 3. Global field power curves of the alcohol-related and neutral NoGo event-related potentials in patients and controls. The colored time windows denote microstates of the N2 and P3 complexes. alcNoGO, alcohol-related NoGo; neuNoGo, neutral NoGo.

NoGo type between 432 and 488 ms and between 492 and 518 ms. To investigate whether this effect was a NoGo-type effect or more general picture-type effect, the analysis was rerun on the Go-ERPs. The effect was replicated, which indicated that it was due to the picture type in general and not to context-specific inhibition.

Analyses with Group as the Between-Subjects Factor

A Ragu analysis with group (patients, controls) and NoGo-type (alcNoGo, neuNoGo) factors yielded the following effects.

NoGo-N2

Effects on Map Strength and Topography. No significant results were found.

NoGo-P3

Effects on Map Strength. There was a main effect of group between 420 and 494 ms (76 ms) because the controls had higher GFP than the patients. The main effect of group was replicated in the post hoc analyses, which included Go-ERPs, and no interaction in the respective time frame was observed. The effect therefore depended on the general attenuation of the P3 amplitude in the patients with AUD, irrespective of picture type or Go type.

Topographic Effects. The only significant effect found in this analysis was the effect of NoGo type between 430 and 518 ms. As reported above (see topographic P3 effects in the analysis with OCDS as the between-subjects factor), this effect was also present in the Go trials and was attributed to a general effect of picture type.

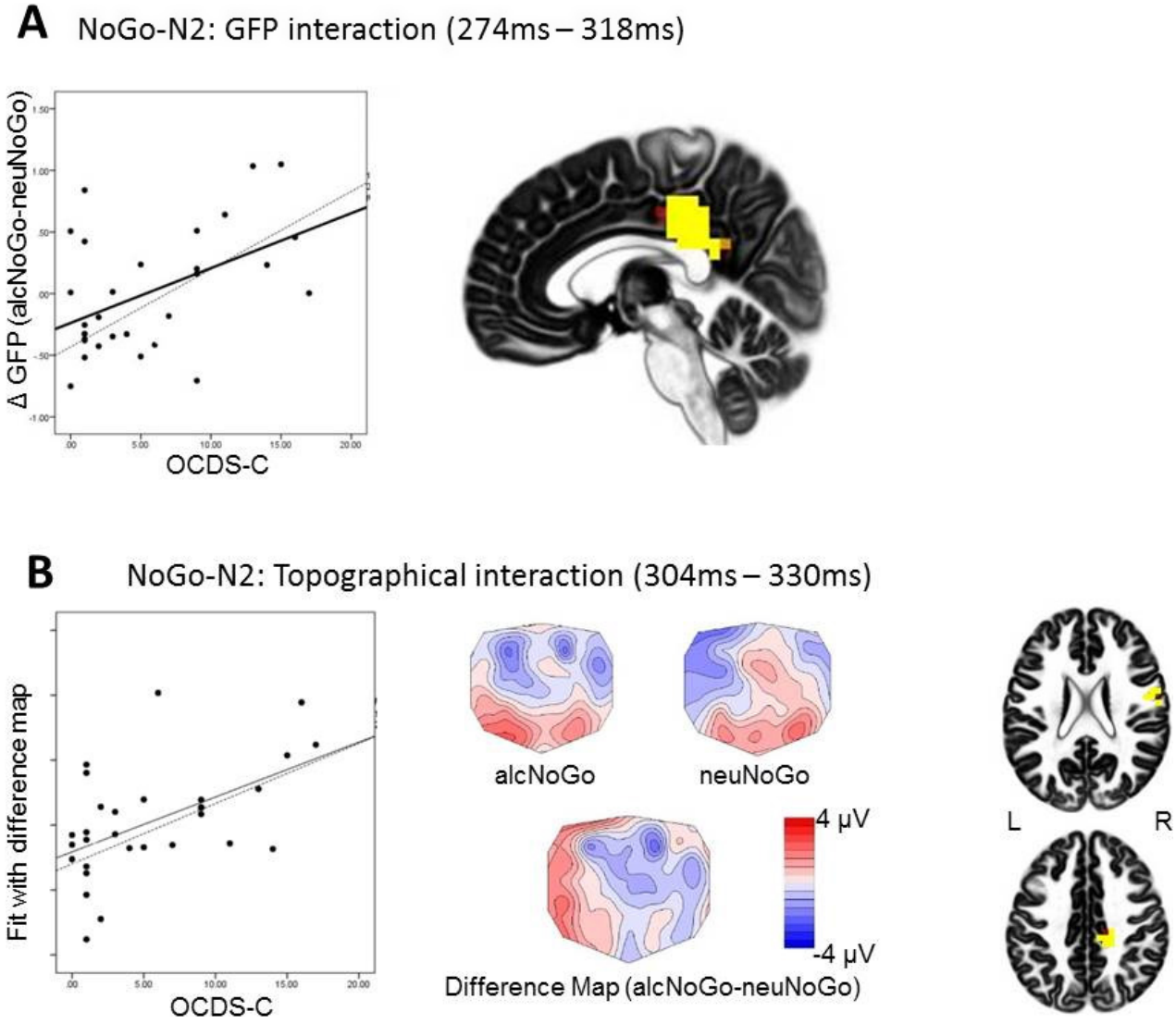

Fig. 4. Illustration of the OCDS-C by NoGo-type interaction in the NoGo-N2 component. (**A**) Effect on map strength (GFP) between 274 and 318 ms. Left: GFP difference between alcohol-related and neutral NoGo trials (calculated in individual ERPs) plotted against individual OCDS-C scores. The thick line represents the linear relationship for the whole group (patients and controls, $p = 0.039$, $r = 0.38$), and the dashed line represents an even stronger association when analyses were restricted to patients ($p = 0.01$, $r = 0.64$). Right: sLORETA source analysis of the effect yielded a large cluster in the PCC, corrected for multiple comparisons). (**B**) Effect on map topography between 304 and 330 ms. Left: Fit with the difference map (calculated in individual ERPs) plotted against individual OCDS-C scores. The thick line represents the linear relationship for all subjects (patients and controls, $p = 0.006$, $r = 0.49$), and the dashed line represents the association when the analyses were restricted to patients ($p = 0.002$, $r = 0.72$). Middle: Illustration of the topographical effect: During neutral NoGo trials, subjects with high OCDS-C values displayed a right-lateralized parieto-occipital maximum, while the topography during alcohol-related NoGo-ERPs was characterized by a bilateral (or left-lateralized) maximum. The difference map between these 2 topographies is shown below. Right: sLORETA source analysis of the effect replicated the PCC cluster (lower picture) and yielded an additional cluster in the premotor cortex (BA 6, upper picture; uncorrected for multiple comparisons). GFP, global field power (map strength); OCDS-C, compulsion subscale of Obsessive Compulsive Drinking Scale; alcNoGO, alcohol-related NoGo; neuNoGo, neutral NoGo; ms, milliseconds; ERP, event-related potentials; PCC, posterior cingulate cortex.

Source Analysis with sLORETA

Effects in the NoGo-N2. Interaction Between OCDS-C and NoGo Type (GFP)—To identify the neural generators of the GFP interaction between NoGo type and OCDS-C in the N2, CDR values were averaged from 274 to 318 ms and subjected to a voxel-wise correlational analysis examining the association between the paired contrast (alcNoGo minus neuNoGo) of the CDR values and OCDS-C. Using an alpha level of 5% (statistical nonparametric mapping-defined threshold of $r = 0.678$), this analysis yielded a large cluster in the right posterior cingulate cortex (PCC) with a cluster center in BA 31 and spanning parts of BA 23 and 24 and single voxels in BA 5 and 7 (cluster maximum [MNI]: 15/−35/40; cluster extent: 45 voxels, see Fig. 4*A*). In this cluster, the activation difference (with higher activation in alcNoGo trials than in NeuNoGo trials) increased with increasing OCDS-C

values. This localization was replicated when the analyses were restricted to the patient group only.

Interaction Between OCDS-C and NoGo Type (Topography)—To investigate the generators of the topographical effect within the N2 time frame, a similar regression analysis of the normalized CDR values (averaged from 304 to 330 ms) was performed. At a corrected alpha level of 5%, the analysis did not yield significant results. However, because significance was already established on the scalp topography level and topographical differences inevitably originate from differences in underlying generators, we lowered the statistical threshold to $p_{\text{uncor.}} \leq 0.001$ (uncorrected for multiple comparisons, threshold of $r = 0.57$, clusters with a size ≥ 25 mm^2 were reported). With this uncorrected statistical threshold, the analysis yielded 2 clusters in which the activation difference (with higher activation in alcohol-related NoGo trials than in neutral NoGo trials) increased with higher OCDS values (Fig. 4*B*). Similar to the localization of the GFP effect, there was a cluster in the right PCC (BA 31, cluster maximum [MNI]: 20/−30/40; cluster extent: 6 voxels). The second cluster was centered in the premotor area (BA 6, right precentral gyrus, cluster maximum [MNI]: 55/−5/25; cluster extent: 7 voxels, with single voxels in BA 4 and BA 9).

DISCUSSION

The present study assessed the neurophysiological correlates of inhibition in patients with AUD and healthy controls in alcohol-related and neutral contexts. We hypothesized that response inhibition in alcohol-related contexts would enhance conflict in patients with AUD, which would be reflected in an enhanced N2 component and modulated by subjective craving. Interestingly, the difference between alcohol-related and neutral NoGo trials was affected by subjective craving (indicated by a strong OCDS by NoGo-type interaction) rather than by the diagnostic category (no group by NoGo-type interaction). This observation suggests that individual parameters exert a stronger influence on this neurophysiological response than the diagnostic category does and that the enhanced conflict during alcohol-related NoGo trials, which is reflected in the N2, is primarily related to the amount of subjective craving.

The few prior studies that examined context-specific inhibition in social drinkers (Petit et al., 2012) or patients with AUD (Petit et al., 2014) also did not report significant group by context interactions, which is in line with our findings. The impact of craving on context-specific inhibition has so far been investigated only in social drinkers (Petit et al., 2012). However, in contrast to our results, no interaction was observed. Besides this difference in the investigated sample, there are also differences in task design and electrophysiological methodology which might account for this inconsistency. First, the Go/NoGo ratio in the present study was considerably higher (8 here vs. 2.3 in Petit et al., 2012, 2014) which probably created a stronger tendency to respond. Furthermore, 2 different alcohol-related pictures were used in Petit and colleagues (2012, 2014), while the present study used 60 different alcohol-related pictures, which might have prevented habituation effects from minimizing the contextual differences. Considering electrophysiological methodology, Petit and colleagues (2012, 2014) compared ERP amplitudes from 6 fronto-parieto-central electrodes at individually defined peak latencies, while our study examined 70 electrodes distributed over the entire scalp and analyzed the entire time period of the NoGo-N2 component. The interaction effects observed here spanned the second half of the N2 component rather than the peak latency. Thus, the enhanced conflict seemed to prolong N2 activation rather than merely enhancing the peak.

Generators of the GFP interaction and subsequent topographic effects were estimated to be located in the PCC, where subjects with high levels of craving displayed greater differences in the activation levels between the alcohol-related and neutral NoGo trials compared with subjects with low craving levels. These findings suggest that in subjects experiencing high levels of craving, the PCC is activated more (indicated by the GFP interaction) and longer (indicated by the topographic interaction) in alcohol-related NoGo trials than in neutral ones. The enhanced PCC activation to alcohol-related cues is among the brain regions that most clearly differentiate patients with AUD from control subjects (Schacht et al., 2013). It varies with the severity of alcohol addiction (Claus et al., 2011) and amount of alcohol consumption in patients with AUD (Tapert et al., 2003) and risky drinkers (Bragulat et al., 2008). A relationship between craving and PCC activation has been observed in tobacco smokers (Kuhn and Gallinat, 2011) and patients with AUD (Courtney and Ray, 2014). Even more interesting in the present context is that enhanced PCC activation has been observed when smokers resisted craving induced by cigarette cues compared to simply attending to the pictures (Brody et al., 2007). There is no single well-accepted theory of PCC function. Consistent with its prominent involvement in the default mode network, PCC activity has been related to internally directed thoughts (Buckner et al., 2008), autobiographical memory processes (Svoboda et al., 2006), and retrieval of intentions (Cona et al., 2015). Other approaches have interpreted task-related PCC activation in terms of the subjective perception of emotional salience and reward (Kable and Glimcher, 2007; Maddock et al., 2003) or risky decision making (Hayden et al., 2008). To account for PCC involvement in such a variety of contexts, PCC has been proposed to be responsible for the dynamic and endogenously driven adaptation of decision-making strategies (Pearson et al., 2011) and, thus, for subjectively adaptive behavior. Our demonstration of a PCC-driven interaction effect in the N2 might thus reflect the fact that differences in subjective and endogenously generated salience attribution require stronger effort in strategy updating during alcohol-related NoGo trials in subjects with high OCDS values. This interpretation is also in line with addiction models postulating

that enhanced activation in networks involved in memory and salience attribution lead to a strong urge to consume, which then has to be inhibited by an (often weakened) executive control system (Volkow and Baler, 2014). Furthermore, source localization of the topographic effect indicated that, in addition to the PCC cluster, activation of the right premotor cortex increased differentially during alcNoGo trials in subjects with high OCDS values, thus suggesting that successful response inhibition (Menon et al., 2001; Sylvester et al., 2003) during alcohol-related trials requires more resources. One might argue that alcohol craving is by definition unique to patients with alcohol-related disorders and thus cannot be reasonably measured in healthy controls. Even though there are also strong arguments for conceptualizing craving as a continuum (e.g., Sinha, 2013), we considered this view and repeated the analyses in the patient group only, and replicated the effects.

In the P3 component, we observed no such interaction but replicated the group difference resulting from the higher GFP in the controls compared with the patients with AUD. Thus, in contrast to the N2 enhancement in alcohol-related contexts, which strongly varied with individual characteristics, the P3 did not vary with context or subjective craving but rather changed with the diagnostic classification. Lower P3 might thus be interpreted as an AUD marker or, as has been suggested by reports of attenuated P3 in relatives of patients with AUD (Kamarajan et al., 2005b), a predisposition to develop substance-related problems. It is noteworthy that the lower P3 amplitudes were not restricted to a specific picture type (alcohol-related or neutral) or Go type (NoGo or Go) but was present in all ERPs of the patients with AUD. This finding is consistent with prior reports that demonstrated lower P3 in a variety of different tasks (Porjesz et al., 2005).

Behaviorally, the patients showed slower RTs on alcohol-related compared with neutral Go trials, and this difference was not significant in the control group. This effect might reflect either active disengagement strategies that patients with AUD who are currently trying to stay abstinent employ when confronted with alcohol-related stimuli (Noel et al., 2006), or alternatively, it might indicate a proactive inhibition strategy that they adopt to prevent EOCs in NoGo trials (Verbruggen et al., 2014). This account is in line with the (nonsignificant) observation that patients made slightly less errors on alcohol-related NoGo trials than on neutral NoGo trials.

In contrast to earlier reports (Smith et al., 2014), we did not observe significant differences in the error rates. Even if this behavioral noneffect might have theoretically resulted from the small sample size, which is an overall limitation of our study, the descriptive numbers indicated that the difference between the groups was quite small (see Table 4*A*). In the absence of behavioral NoGo effects, the electrophysiological findings reported above seem not to be due to differences in task performance.

One study limitation is the rather small sample size, which challenges the generalizability of the results and limits the statistical power (to 0.7), thus increasing the risk of β-errors. Furthermore, some important and interesting parameters describing the patient group are missing. In addition, the matching could have been improved with groups differing in education and (albeit not significantly) in gender (but note that additional analyses, which are reported in the Supporting Information, showed that the results were not influenced by these variables).

To conclude, this study replicated the observation of a lower P3 in subjects with AUD. Moreover, our results demonstrated that, in subjects prone to craving, alcohol-related contexts lead to enhanced and prolonged activation of the PCC and premotor areas during the time frame of the N2 component. This additional brain activation is probably due to enhanced salience attribution making response strategy updating and response inhibition during NoGo trials in the alcohol-related context more effortful in subjects with strong craving. This context-specific effect was not observed in the group comparisons (patients with AUD vs. controls) but was strongly linked to the individual amounts of craving.

Our findings emphasize the relevance of craving, which was recently added to the diagnostic criteria for AUD in the DSM-5, for the understanding and treatment of AUD beyond the diagnostic category. The patients' conscious experience of strong craving is reflected in the (unconscious) neurophysiological response indicating stronger conflict when confronted with alcohol-related cues. This conflict probably makes it more difficult for patients with strong craving to successfully inhibit drinking urges in these situations than for patients with low subjective craving. In consideration of this particularity, treatment might be individually tailored to meet the needs of this subgroup. For example, these patients may especially profit from (i) consciously learned coping skills for situations characterized by high craving and (ii) training interventions that are specifically tailored to target altered processes on a subconscious level (such as cognitive bias modification or inhibition training). As a general conclusion, our results underline the importance of realistic, alcohol-related stimuli in AUD treatment and research because such stimuli evoke distinct neurophysiological responses and are particularly relevant for patients with AUD.

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AUTHORS CONTRIBUTIONS

MS, FM, and WF designed the study. MS, WF, and JO acquired the data. MS, TK, WF, and JO analyzed the data.

MS, TK, and FM interpreted the data. MS wrote the first draft of the manuscript. All authors critically reviewed and approved the final manuscript.

CONFLICT OF INTEREST

The authors have no conflict of interests to declare.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article:

Data S1. Additional information on procedure, task, patients, microstate analysis, and potential effects of education and gender.