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The neural correlates of priming emotion and reward systems for conflict processing in alcoholics

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Abstract

Emotional dysregulation in alcoholism (ALC) may result from disturbed inhibitory mechanisms. We therefore tested emotion and alcohol cue reactivity and inhibitory processes using negative priming. To test the neural correlates of cue reactivity and negative priming, 26 ALC and 26 age-matched controls underwent functional MRI performing a Stroop color match-to-sample task. In cue reactivity trials, task-irrelevant emotion and alcohol-related pictures were interspersed between color samples and color words. In negative priming trials, pictures primed the semantic content of an alcohol or emotion Stroop word. Behaviorally, both groups showed response facilitation to picture cue trials and response inhibition to primed trials. For cue reactivity to emotion and alcohol pictures, ALC showed midbrain-limbic activation. By contrast, controls activated frontoparietal executive control regions. Greater midbrain-hippocampal activation in ALC correlated with higher amounts of lifetime alcohol consumption and higher anxiety. With negative priming, ALC exhibited frontal cortical but not midbrain-hippocampal activation, similar to the pattern observed in controls. Higher frontal activation to alcohol-priming correlated with less craving and to emotion-priming with fewer depressive symptoms. The findings suggest that neurofunctional systems in ALC can be primed to deal with upcoming emotion- and alcohol-related conflict and can overcome the prepotent midbrain-limbic cue reactivity response.

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Conflict of interest Authors Tilman Schulte, Young-Chul (Eugene) Jung, Edith V. Sullivan, Adolf Pfefferbaum, Matthew Serventi. and Eva M. Müller-Oehring declare that they have no conflict of interest.

Compliance with Ethical Standards

Informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

Keywords

Alcohol and emotion; Cue reactivity; Executive control; Functional MRI; Midbrain-limbic; Priming

Introduction

Chronic alcoholism is associated with difficulty in exerting executive control of behavior when faced with choices involving reward and emotion (Müller-Oehring et al. 2013). The rewarding effects of alcohol are transmitted via projections in the mesolimbic corticostriatal system that originates in midbrain structures (Berridge and Robinson 2003; Di Chiara 2002). These midbrain-based reward circuits become hypersensitive to alcohol cues (Robinson and Berridge 2008) as alcohol cue-reactivity develops through personal alcohol use (Pulido et al. 2009), and the rewarding effects of alcohol become more enstated during the progression of alcohol addiction (King et al. 2015). Consequently, alcohol cues induce physiological cue reactivity and craving in alcohol-dependent individuals in laboratory and real-world situations (Witteman et al. 2015). In alcoholics (ALC), reward-related cues can activate limbic-striatal regions (Schacht et al. 2011), associated with conditioned appetitive responses and reward learning (Cole et al. 2015), and visual extrastriate regions, associated with an attentional bias to alcohol-associated cues (Vollstädt-Klein et al. 2011). Recent functional magnetic resonance imaging (fMRI) studies report associations between neural cue-reactivity in mesolimbic pathways and craving or relapse (Bach et al. 2015; Grüsser et al. 2004; Kirsch et al. 2015; Schacht et al. 2013).

Neuroimaging studies of alcohol addiction further suggest closely interacting neural systems in the processing of negative emotion and alcohol-related information (Alba-Ferrara et al. 2016). Limbic (amygdala, nucleus accumbens, thalamus, hippocampus) and cortical regions interact when evaluating current relevance of intrinsically salient stimuli, e.g., aggressive or fearful faces, for further processing, suppression (Troiani and Schultz 2013), or subsequent initiation of appropriate behavior (Namburi et al. 2016; Vogt et al. 2011). This interaction represents a basic mechanism responsible for regulating stimulus-driven responses and attentional guidance towards objects of relevance or need, and for exerting executive control over reward and emotional challenges (Müller-Oehring and Schulte 2014). For example, alcohol-dependent men showed attenuated cortical–limbic–striatal responses to anticipatory anxiety indicating a lack of engagement of neural mechanisms that regulate emotion in stress situations (Yang et al. 2013). Automatic allocation of attention to salient stimuli is guided by a person’s individual goals or needs (Vogt et al. 2010) and can be driven by alcohol-related stimulus attributes in ALC (Klein et al. 2013; Alba-Ferrara et al. 2016) promoting the initiation of alcohol consumption (Weafer and Fillmore 2013) or triggering relapse in abstinent alcoholics (Grüsser et al. 2004; Cooney et al. 1997). Neural dysregulation of the overlapping emotion and addiction systems together with the difficulty to engage executive control mechanisms can put alcohol-dependent individuals at risk for relapse when cortical–limbic–striatal systems are activated by either alcohol cues (e.g., Courtney et al. 2015; Cyders et al. 2014) or emotional events (e.g., Charlet et al. 2014).

Alcoholism can disrupt brain activity in regions subserving executive control of behavior influencing choices involving alcohol (Bjork et al. 2004; Montgomery et al. 2012; Noël et al. 2012; Noël et al. 2013; Pitel et al. 2007). fMRI studies reported that more years of chronic alcohol consumption negatively affected fronto-parietal brain connectivity of the executive control system in ALC (Weiland et al. 2014). Similarly, lower dorsolateral prefrontal cortical (dlPFC) activation in ALC during a response inhibition task was associated with a greater urge to drink (Li et al. 2009). Further, we have found evidence for a role of midbrain-based reward systems to interact with frontoparietal executive control systems in ALC using Stroop Match-to-Sample task-activated fMRI probing executive control and automatic response functions arising from repetition learning (Schulte et al. 2012). We accordingly devised an alcohol-emotion Stroop Match-to-Sample fMRI task (Müller-Oehring et al. 2013) requiring inhibition of emotion and alcohol-related Stroop word content and found evidence for activation of midbrain-limbic reward and emotion systems to alcohol-related Stroop conflict while dlPFC executive control regions were less activated in ALC.

The ability to process conflict between stimulus attributes (e.g., between a word's ink color and its content) is impaired in ALC (Kovacevic et al. 2012; Pitel et al. 2007; Schulte et al. 2005; Schulte et al. 2012). It involves directing attention selectively and suppressing irrelevant information, which is essential for making decisions (Broadbent 1958; Broadbent and Gathercole 1990). Guiding attentional selection to enhance inhibitory processes has been shown with negative priming (Frings et al. 2008; Frings et al. 2015): when an irrelevant object is ignored, subsequent responses to an object of the same semantic category are slower (Tipper 1985, 2001). This phenomenon may be explained by the spreading of inhibition to semantically related objects, that is, when participants ignored a stimulus, the representation of this stimulus should become inhibited and all semantically related attributes following immediately after presentation of a prime should also become inhibited (Anderson 1983; Hutchison 2002). As the inhibition of automatic responses to alcohol or emotion constitutes a core deficit in individuals with alcohol addiction (e.g., Moeller et al. 2016), the exposure to stress, emotion, and alcohol cues can trigger relapse in abstinent alcoholics (Cooney et al. 1997; Fox et al. 2008; Heinz et al. 2016). Thus, enhancing an individual's inhibitory potential through semantic priming could be an initial step in regaining control and, if applicable in addiction rehabilitation medicine, may ultimately strengthen response inhibition mechanisms and reduce relapse risk.

To test this, we are now posing the question whether such priming can be used to help alcoholics invoke inhibitory mechanisms. Accordingly, we designed a *priming* alcohol and emotion Stroop Match-to-Sample task. Images of alcohol beverages and emotional faces primed the semantic content of an upcoming emotion or alcohol-related Stroop word conflict. Based on the assumption that alcohol cues have gained emotional relevance (cue reactivity) in ALC biasing the brain's evaluation system towards automatic processing of alcohol-related stimulus attributes, even if the information is irrelevant for the task performance, we expected greater midbrain-limbic-striatal activation to alcohol-related and intrinsically salient emotional stimuli (e.g., angry or happy faces) and less frontal cortical executive control system activation in ALC than controls. Second, in Stroop conflict situations when emotion or alcohol-related word content needs to be inhibited, we expected that negative semantic priming will help ALC engage inhibitory frontoparietal executive

control systems and overcome the prepotent midbrain-limbic-striatal cue reactivity response. We further hypothesized that activation strength would be related to measures of 'current relevance or need' in ALC (Troiani and Schultz 2013), e.g., alcohol craving, or alcoholism severity. Specifically, we predicted that frontal activity would be associated with the degree of interference from emotion- and alcohol-related stimulus content, i.e., Stroop conflict, and that striatal-limbic activity to emotion- and alcohol-related cues would be associated with alcoholism severity and craving intensity.

Methods and materials

Participants

Study participants were 26 abstinent chronic alcohol-dependent patients (ALC) and 26 age and sex-matched controls (CTL). Functional neuroimaging data from overlapping samples were published for different tasks (Jung et al. 2014a, b; Müller-Oehring et al. 2013) and resting-state (Müller-Oehring et al. 2015a). Here, we focused on priming neural systems for emotion and alcohol-related conflict processing using a novel 'Priming Alcohol and Emotion' Stroop Match-to-Sample paradigm. ALC participants were recruited from local rehabilitation programs and self-help groups; controls were volunteers from the local community recruited through flyers, announcements, or word of mouth. All subjects underwent a Structural Clinical Interview for DSM-IV (SCID) (American-Psychiatric-Association 2000) to determine the diagnosis of alcohol dependence by consensus of at least two calibrated interviewers (clinical research psychologists, research nurse) and to characterize psychiatric history. History of schizophrenia and bipolar disorders were exclusions; the healthy control group had no current or past Axis 1 psychiatric disorder. Current use of psychoactive medications; history of major neurological or medical disorder, head trauma with loss of consciousness (>30 min), MRI contraindications (e.g., irremovable metal), color-blindness, and non-correctable vision were also exclusions. Although ALC were not necessarily seeking treatment at the time of the study, they had sought treatment at some time during the course of their disease.

Of the 26 ALC, 25 met DSM-IV criteria for alcohol dependence and one for alcohol abuse (who was not an outlier from the ALC group and within the distributions for lifetime alcohol consumption and AUDIT scores); 24 were in early remission (met alcohol dependence criteria for ≥3 months and <12 months); one was in sustained remission (>12 months) by 10 days, i.e., had last met alcohol dependence criteria 375 days ago. Additional clinical scales were administered to quantify alcoholism severity (the Alcohol Use Disorders Identification Test (AUDIT) (Babor et al. 2006)), subjective craving shortly before fMRI acquisition (Short Item Scale Alcohol Craving Questionnaire-Revised (ACQ-R) (Drobes and Thomas 1999; Raabe et al. 2005)), and emotional state (State-Trait Anxiety Inventory (STAI) (Spielberger et al. 1983), Beck Depression Inventory (BDI-II) (Beck et al. 1996)). Here, alcoholics with higher anxiety (STAI-S scores) also reported higher alcohol craving (ACQ-R scores) (ALC: *Rho* = .47, $p = 0.009$; CTL: *Rho* = .02, *ns*). None of the controls and 46 % of ALC met DSM-IV criteria for past drug dependence with cocaine being used most often by 35 % ($n = 9$), amphetamines by 12 % ($n = 3$), and opioids by 12 % ($n = 3$). In all cases alcohol was the drug of choice and alcohol dependence was more recent than drug dependence. The median

numbers of years since last use was as follows: cocaine: 1.3 years; amphetamines: 6.5 years; and opioids: 2 years. Current smokers included 14 ALC and 3 control subjects ($\chi^2(1) = 10.6$, $p = 0.001$). Demographic data, alcohol and substance use history, mood, and premorbid intelligence scores are in Table 1. The groups were matched in handedness and did not differ in visual acuity, body mass index (BMI), and physiological measures (heart rate, blood pressure). Although the ALC had fewer years of education and a lower socioeconomic status (SES) (Hollingshead and Redlich 1958) than controls, both groups had received an average education beyond high school.

Procedure

The study was approved by the Institutional Review Boards at SRI International and Stanford University School of Medicine. All participants gave written informed consent for study participation.

Stimuli and experimental design—All subjects performed the 'Priming emotion and alcohol Stroop Match-to-Sample' task during fMRI acquisition using a clinical whole-body GE 3 T scanner. Stimuli were presented through a rear-projection system and viewed via a mirror attached to the head coil.

Alcohol and emotion priming - Stroop match-to-sample task: The task containing color, word, and picture stimuli was presented with PsyScope software (Cohen et al. 1993) and synchronized with the MRI acquisition via the fORP system interface (www.curdes.com).

A *Stroop match-to-sample:* Similar to previous versions of the Stroop Match-to-Sample task (e.g., Müller-Oehring et al. 2013; Schulte et al. 2012), subjects were instructed to match the color of a sample stimulus displayed for 700 ms in the center of the screen to the font color of a Stroop word stimulus that appeared for 1100 ms thereafter (Fig. 1a). The color samples and Stroop word colors were red, green, or blue. The Stroop word was either congruent (word RED written in *red* font) or incongruent (word RED written in *blue* font). The font color of the Stroop word either matched or did not match the sample color. For color matches, subjects pressed a YES-key and for non-color matches, a NO-key using their dominant hand, thereby providing measures of reaction time and accuracy for each trial. For incongruent-nonmatch color-Stroop conditions, the sample color always matched the word content (e.g., blue sample, word BLUE written in red font color) (Schulte et al. 2005).

In contrast to previous task versions, a picture of an alcoholic beverage, an emotional face (angry, happy) (MacBrain Face Stimulus Set; www.macbrain.org/resources.htm), or neutral gray patch was presented for 700 ms between the color sample and the Stroop word (Fig. 1). This task was designed to study cue reactivity (Fig. 1b) and priming of an upcoming emotion and alcohol-related conflict (Fig. 1c) by using pictures that validly predicted the word's content and to identify processing differences between ALC and controls.

B *Cue reactivity:* To test *cue reactivity* to emotional face and alcohol beverage picture trials (vs. neutral trials), congruent non-conflicting Stroop words were used (Fig. 1b).

C *Priming Stroop:* To test the effect of *priming emotion and alcohol-related conflict,* Stroop words had an alcohol (e.g., BEER, WINE, WHISKEY), emotionally positive (e.g., HAPPY, JOY, GLAD), or negative content (e.g., ANGRY, MAD, FURIOUS); each word was printed in red, blue, or green font color (Fig. 1). The content of the picture always primed the content of the Stroop word, e.g., an angry face preceded the word ANGRY and a picture of a glass of wine preceded the word WINE. The task was to "match colors" and, consequently, the picture prime and Stroop word content were not relevant for accurate performance.

The Stroop word's content (incongruent color: Schulte et al. 2009; emotion: McKenna and Sharma 2004; Pratto and John 1991; reward-related: Hickey et al. 2010; Kirsch et al. 2015) is assumed to be processed automatically and to elicit prepotent responses that need to be inhibited to correctly and efficiently perform the color-matching task. Accordingly, Stroop effects to primed alcohol and emotion Stroop conditions are operationalized to test 'current need or state,' in ALC relative to controls, and to weigh against conditions of 'neutral state' (color) conditions. At the behavioral level, the Stroop effect (interference from the Stroop word's content) is defined as the difference in reaction time (RT) to incongruent and congruent color-word stimuli (Fig. 1a). Similarly, alcohol and emotion Stroop effects were defined as the difference in RT between alcohol/emotion words and congruent color-word stimuli (Fig. 1c), equivalent to previous reports (Müller-Oehring et al. 2013).

As in previous task versions, trials were presented in two block types: response repetition (RR) and response switching (RS) blocks. RR and RS blocks comprised the same 96 match and nonmatch trials, only in a different order: In RS blocks, color match and nonmatch trials were presented in a pseudo-random order and required switching between YES (sample-target colors match) and NO responses (sample-target colors do not match); in RR blocks, either color match (YES responses) or nonmatch trials (NO responses) were presented and did therefore not require response switches. This allowed testing the effect of repetitive behavior on cue reactivity and Stroop effects. To quantify Stroop effects within a block design, incongruent and congruent trials were never mixed within a block. Consistent with our experience with previous task versions of the Stroop Match-to-Sample task (Müller-Oehring et al. 2013; Müller-Oehring et al. 2015a, b; Schulte et al. 2005; Schulte et al. 2011; Schulte et al. 2012), subjects were not aware about the blocked trial design, as indicated in post-scan interviews.

All study participants underwent two runs of the alcohol-emotion priming Stroop match-to-sample task within the same scan session; each run contained 6 stimulation blocks for each condition: alcohol, positive and negative emotion, and color (block = 8TRs; TR = 2.2 s). Total number of trials was 192. All subjects performed a practice session before entering the scanner, and test instructions were reviewed through the scanner's intercom system before each run.

Magnetic resonance imaging (MRI)

Data acquisition and analyses: Subject motion was minimized by following standard practices for head fixation, such as additional padding of the neck and the sides of the head

and use of a head strap. Whole-brain fMRI data were acquired with a T2*-weighted gradient echo-planar pulse sequence (2D axial, TE = 30 ms; TR = 2200 ms; flip angle = 90°; in plane resolution = 3.75 × 3.75mm^2; thick = 5 mm; gap = 0 mm; number of slices = 36; FOV = 240×240mm^2; 1 NEX). A dual-echo fast spin echo (FSE) scan was acquired (2D axial; TR = 5000 ms; TE = 17/102 ms; thick = 5 mm; gap = 0 mm; xy matrix = 256 × 256; flip angle = 90°; number of slices = 36; FOV = 240×240mm^2; 1 NEX) and used for spatially registering the fMRI data.

Image preprocessing and statistical analyses: The fMRI analysis was done with the SPM8 software package (Wellcome Department of Cognitive Neurology, UK; http://www.fil.ion.ucl.ac.uk/spm/) and focused on the whole brain. The functional images were subjected to geometric distortion (field map) correction and the time-series were realigned to the first image as reference image to remove movement artifacts in fMRI (Friston et al. 1995). The FSE structural images were co-registered to the mean unwarped and motion-corrected functional image for each subject and segmented into gray and white matter images. Functional and structural gray matter images were normalized to Montreal Neurological Institute (MNI) space assuring that the fMRI signal was confined to gray matter. Functional volumes were smoothed with a Gaussian kernel of 8 mm (FWHM). Individual statistics were computed using a general linear model (GLM) approach as implemented in SPM8 and using the realignment parameters from each run as confounds (Friston et al. 1995). Statistical preprocessing consisted of high-pass filtering at 70.4 s, low-pass filtering through convolution with the canonical hemodynamic response function, and global scaling.

For first level analysis, one image per contrast was computed from a design matrix that included the task conditions as explanatory variables in addition to the estimated individual movement parameters as regressors. *Cue reactivity* contrasts of interest were derived at the individual analysis level for non-conflict trials (Fig. 1b): for *Alcohol* by contrasting alcohol beverage pictures to congruent (alcpic > con) conditions, for *Positive-Emotion* by contrasting happy face pictures to congruent (pospic > con) conditions, and for *Negative-Emotion* by contrasting angry face pictures to congruent (negpic > con) conditions. *Priming Stroop conflict* contrasts of interest were derived for alcohol and emotion word conflict trials (Fig. 1c): for *Alcohol Stroop* by contrasting alcohol to congruent (alc > con) conditions, for *Positive-Emotion Stroop* by contrasting positive emotion to congruent (pos > con) conditions, and for *Negative-Emotion Stroop* by contrasting positive emotion to congruent (neg > con) conditions. In addition, individual *color* Stroop contrasts, derived by contrasting incongruent to congruent color-word (inc > con) conditions (Fig. 1a), were added to the model for comparison (see also Müller-Oehring et al. 2013). The individual contrast images were then subjected to random effects analyses for group averaging and population inference.

The second level design matrix involved two factorial models, each with 2 factors, which were for *cue reactivity*: group (ALC, CTL) and picture cue (alcohol beverage, happy faces, angry faces), and for *priming Stroop*: group (ALC, CTL) and Stroop (color, alcohol, positive emotion, negative emotion), and their interaction (Friston et al. 2005; Nichols et al. 2005). Whole brain corrected *p*-thresholds for combined spatial extent and peak intensity (see also

Poline et al. 1997) were set at $p_{corrected} < 0.05$ and calculated with 3dClustSim (https://afni.nimh.nih.gov/pub/dist/doc/program_help/3dClustSim.html) (see also Eklund et al. 2016).

Statistical analyses—Data analysis of Stroop task performance was conducted with the statistical software package SPSS Statistics 23.0. Repeated measures analysis of variance (ANOVA) tested group effects (ALC, controls) for cue reactivity, color-word Stroop and primed alcohol-emotion Stroop. The alpha p level was set to 0.05. To test our directional hypothesis, where 'current relevance or need' in ALC (addiction severity, craving) would correlate with more cue reactivity and difficulty in executive control (greater Stroop conflict), we used one-tailed Spearman Rho correlation (SPSS 23.0 software package). We extracted individual MR signal change from significant clusters in frontal, and midbrain-limbic-striatal regions (see Tables 2–4) using the matlab-based SPM-compatible MarsBar toolbox (http://marsbar.sourceforge.net/marsbar.pdf). These values were then read into SPSS to test our specific brain-behavior hypothesis that midbrain-limbic-striatal activity to emotion-and alcohol-related cues would be associated with craving intensity or addiction severity in ALC, and that frontal activity would be associated with the degree of interference from emotion- and alcohol-related stimulus content, i.e., primed Stroop conflict, and extrastriate activation with less primed Stroop conflict. Significant voxel cluster of activation, specific to each contrast, were correlated with the respective behavioral effect (e.g., for cue reactivity or primed Stroop effects) and mood scores (anxiety, BDI), and in ALC with alcohol data (lifetime alcohol consumption, alcohol severity, craving). Family-wise Bonferroni correction for 6 comparisons required p levels between $p \leq 0.016$ (for directed hypothesis, 1-tailed) and $p \leq .008$ (2-tailed).

Results

Behavioral scores: alcohol and emotion priming Stroop match-to-sample task

Groups did not differ in overall processing speed (mean RTs; ALC 782 ± 141 ms; CTL 760 ± 138 ms; $F(1,50) = 0.58$, *ns*), but ALC committed more errors than controls (ALC 12.5 ± 13.7; CTL 4.6 ± 4.9; $F(1,50) = 7.64$, $p = 0.008$). Speed and accuracy (error rate) were not significantly correlated in either group (ALC $r = .24$, *ns*; CTL $r = .11$, *ns*), reflecting absence of a speed-accuracy trade-off (Schouten and Bekker 1967). More errors were committed for Stroop word interference (e.g., the word BEER written in blue) than 'congruent' no-interference conditions (the word BLUE written in blue) (Stroop main effect: $F(1,50) = 5.98$, $p = 0.018$) with more errors for the alcohol than emotion conditions (Stroop-by-alcohol/emotion condition interaction: $F(1,50) = 4.85$, $p = 0.032$) as revealed by an ANOVA with Stroop (word interference vs. no-interference), content (alcohol, negative and positive emotion) and group (ALC, CTL) as factors.

Cue reactivity—Repeated measures ANOVA tested for group differences (ALC, CTL) in behavioral cue reactivity (Diff. RTs for alcohol beverage, happy face, angry face conditions) in non-conflict congruent word trials and response block (RR, RS). We found a trend for an alcohol-emotion cue reactivity effect ($F(1,48) = 3.01$, $p = 0.089$), i.e., somewhat greater response facilitation for alcohol beverage than positive emotional face picture trials, and a

significant main effect for response block with response facilitation for response repetitions (RR) and inhibition for response switches (RS) ($F(1,48) = 9.42$, $p = 0.004$) (Fig. 2a). No group effect or group-by-condition interaction was observed (all $p > 0.05$). As hypothesized, within the group of alcoholics, higher alcohol craving (ACQ-R scores) correlated with behavioral cue reactivity to alcohol beverage pictures (Diff. $RT_{alcpic\text{-}con}$) (*Rho* = 0.48, $p = 0.009$).

Executive control—We tested whether groups differed in color-word interference, the 'original' Stroop effect, defined as the difference in reaction time between incongruent and congruent color words (diff. $RT_{INC\text{-}CON}$) (see Fig. 2b, left). Both groups, showed color-word interference, i.e., longer RTs to incongruent than congruent Stroop color-words (Stroop main effect: $F(1,47) = 14.06$, $p < 0.0001$), and faster RTs to repetition (RR) than switching (RS) (response block main effect: $F(1,47) = 6.53$, $p = 0.014$). ALC exhibited a trend for greater color-Stroop interference than controls (group-by-Stroop interaction: $F(1,47) = 3.03$, $p = 0.088$), specifically during response repetition (Stroop-RR: $F(1,49) = 4.59$, $p = 0.037$) (Stroop-RS: $F(1,49) = 0.19$, *ns*) (Müller-Oehring et al. 2013).

Priming alcohol-emotion Stroop—Using repeated measures ANOVA with group (ALC, CTL) as between subjects factor, primed Stroop effects (Diff RTs) for each condition (alcohol, positive emotion, negative emotion) and response block (RR, RS) as within subject factor, revealed a significant main effect for primed alcohol-emotion Stroop ($F(1,45) = 6.41$, $p = 0.015$). Here, greater interference was observed from alcohol than negative emotion conditions (Diff. $RT_{alc\text{-}con}$ > Diff. $RT_{neg\text{-}con}$: mean difference 23.7, $p = 0.015$ adjusted for multiple comparisons) as was a main effect for response block ($F(1,45) = 5.80$, $p = 0.02$) with more interference during response switching than repetition. Overall, groups exhibited similar primed alcohol and emotion Stroop effects ($F(1,45) = 1.448$, *ns*). ANOVAs conducted for RR and RS conditions separately showed a trend for greater primed alcohol-emotion Stroop interference in ALC than CTL during response repetitions (Primed Stroop-RR: $F(1,46) = 3.58$, $p = 0.066$; primed Stroop-RS: $F(1,48) = 0.01$, *ns*) (Fig. 2b).

Functional neuroimaging results

Cue reactivity—We examined cue reactivity contrast activation maps for ALC and CTL for alcohol beverage (alcpic > con) and happy face (pospic > con) and angry face (negpic > con) pictures in non-conflict congruent word conditions (Fig. 1b). For alcohol and emotion cue conditions, ALC engaged a midbrain-limbic network, whereas CTL engaged a mainly medial frontoparietal network (Table 2), a pattern that was significantly different between the groups as tested with group contrast analysis (Table 3). In addition, ALC showed more cerebellar activation than controls in response to emotion and alcohol cues. A MANCOVA with group (ALC, CTL) as between subject factor and education (years), SES, number of errors, and smoking status as covariates confirmed significant group activation differences for all clusters (Table 3). A significant group-by-condition interaction effect revealed that ALC, relative to controls, activated a medial frontoparietal attentional control network less to alcohol beverages than to angry face pictures (Table 3, Fig. 3a). Again, repeated measures ANCOVAs with education (years), SES, number of errors, and smoking status as covariates confirmed group-by-condition interactions.

Correlation with behavior: Consistent with our hypothesis, behavioral *alcohol cue reactivity* (diff. $RT_{alcpic–con\ for\ RS}$) correlated with greater midbrain-limbic activity in ALC (midbrain *Rho* = .46, $p = 0.011$; parahippocampus *Rho* = .44, $p = 0.014$; insula $r = .48$, $p = 0.008$; CTL: midbrain *Rho* = −.06, *ns*; parahippocampus *Rho* = −.15, *ns*; insula $r = -.19$, *ns*) and in CTL with greater frontal cortical activity (R. SFG/SMA *Rho* = .53, $p = 0.003$; ALC: *Rho* = −.04, *ns*) (Fig. 3b). Similarly, behavioral *happy face cue reactivity* (diff. $RT_{pospic–con\ for\ RS}$) in ALC correlated with greater midbrain-hippocampal activity (ALC: *Rho* = .46, $p = 0.011$; CTL: *Rho* = −.25, *ns*) and less medial prefrontal activity (ALC: *Rho* = −.50, $p = 0.006$; CTL: *Rho* = .01, *ns).* Accuracy (error rate) of task performance was not significantly correlated with cue-induced activation pattern in either group (all p's > 0.05).

Correlation with clinical data: We tested whether measures of 'alcohol relevance or need' (addiction severity, craving) contributed to explaining neural cue reactivity to alcohol beverage pictures. Greater amounts of lifetime alcohol consumption correlated moderately with midbrain-limbic activity to *alcohol beverage cues* (alcpic > con) (ALC: parahippocampus *Rho* = .41, $p = 0.02$; CTL: *Rho* = −.04, *ns*) (Fig. 3b). Testing relationships between neural cue reactivity to emotional faces and mood measures (BDI, STAI-T), we found greater midbrain-hippocampal activation to *angry faces* in ALC who reported higher anxiety (pospic > con: hippocampus *Rho* = .50, $p = 0.005$; midbrain *Rho* = .44, $p = 0.014$; negpic > con: hippocampus *Rho* = .59, $p = 0.001$; midbrain *Rho* = .63, $p = 0.001$; CTL: all p > 0.05). Further, greater insula activation to *happy faces* (pospic > con) in ALC correlated with fewer depressive symptoms (*Rho* = −.45, $p = 0.014$; CTL: *Rho* = −.31, *ns*) (Fig. 3b).

Executive control—As expected, processing color-word Stroop interference (inc > con) engaged a frontoparietal executive control network with bilateral dorsolateral prefrontal cortex (dlPFC) activation (Fig. 4, upper panel) that was related to behavioral color-word Stroop conflict in CTL (L. dlPFC *Rho* = .47, $p = 0.007$, R. dlPFC *Rho* = .52, $p = 0.003$; ALC: L. dlPFC *Rho* = .07, *ns,* R. dlPFC *Rho* = .01, *ns*) (Fig. 4b).

Priming alcohol-emotion Stroop—Primed *alcohol Stroop* (alc > con) processing engaged a striatal-frontoparietal network including bilateral caudate nuclei, anterior cingulate (ACC), left dlPFC, and left parietal cortices. Primed *emotion Stroop* (pos > con, neg > con) processing mainly engaged left lateralized frontal cortical regions (Table 4a, Fig. 4a upper panel; see Table S1 in Supplement for within-group activations). Group contrast analyses for primed Stroop (alcohol, positive emotion, negative emotion) revealed that ALC activated extrastriate brain regions more than CTL when processing positive emotion Stroop words primed with happy faces, but engaged extrastriate cortices less than CTL for alcohol-related Stroop words primed with alcohol beverage pictures. ALC further exhibited more left hippocampal, right pallidal, and less bilateral thalamic activity to primed negative emotion Stroop than CTL (Table 4b, Fig. 4a lower panel). A MANCOVA with group (ALC, CTL) as between subject factor and education (years), SES score, number of errors, and smoking status as covariates confirmed significant activation differences between groups for all clusters (Table 4b).

Correlation with behavior: For primed negative emotion Stroop, the higher pallidum activation in ALC correlated with greater behavioral Stroop effects (Diff. $RT_{neg\text{-}con\ RR}$) (ALC: *Rho* = .65, $p = 0.001$; CTL: *Rho* = −.26, *ns*), whereas in CTL the higher thalamus, dlPFC, and ACC activation correlated with greater behavioral Stroop effects (Diff. $RT_{neg\text{-}con\ RS}$) (CTL: thalamus *Rho* = .48, $p = 0.007$; dlPFC *Rho* = .44, $p = 0.012$; ACC *Rho* = .46, $p = 0.008$; ALC: thalamus *Rho* = −.26, dlPFC *Rho* = .16, ACC *Rho* = −.04, all *p's* > 0.05) (Fig. 4b). Error rate was not significantly correlated with any activation pattern during primed Stroop processing in either group.

Correlation with clinical data: As hypothesized, during primed alcohol conflict processing, greater striatal activation in ALC correlated with alcoholism severity (higher AUDIT scores) (*Rho* = .44, $p = 0.013$) and lower frontal activity with more craving (ACC *Rho* = −.37, $p = 0.032$); lower extrastriate activity was associated with fewer depressive symptoms (*Rho* = .41, $p = 0.022$). ALC with lower frontal activation during negative emotion conflict processing also reported more depressive symptoms (ACC *Rho* = −.49 $p = 0.008$) (Fig. 4b).

Discussion

Using functional MR imaging, we asked whether negative semantic priming of emotion and alcohol-related conflict could promote inhibition of alcohol-related information in chronic alcoholics and enable neural activation of executive control functions similar to that of controls (Kamarajan et al. 2005; Lawrence et al. 2009; Zack et al. 2011). We had previously observed a predominant midbrain-limbic activation in ALC in contrast to a frontoparietal activation in controls during the processing of alcohol- and emotion-related conflict using an alcohol-emotion Stroop Match-to-Sample task (Müller-Oehring et al. 2013) that was similar to the one used in this study but without semantic priming. Now, in this study, we observed the same midbrain-limbic activation pattern in ALC in response to alcohol beverage and emotional face pictures, embedded in the color-matching task (for non-conflict conditions) and irrelevant for task performance. Thus, independent of whether the emotion and alcohol-related information was presented in the form of a Stroop word's content (Müller-Oehring et al. 2013) or a picture (cue reactivity task), the prepotent automatic neural response in ALC was to engage midbrain-limbic reward systems. By contrast, controls activated frontoparietal systems for inhibitory control over distracting emotion and alcohol-related information while performing the color matching task (see also Gladwin et al. 2013). This finding is consistent with our hypothesis that the brain's evaluation system determines whether a stimulus is processed further or suppressed depending on its relevance to the individual (Courtney et al. 2013; Kamarajan et al. 2005; Li et al. 2009; for a review Müller-Oehring and Schulte 2014).

Critically, the behavioral performance did not differ between groups. Both showed response facilitation to picture trials with alcohol beverage and emotional face cues that was prominent during response repetition (RR) blocks enabling repetition learning, but not during RS blocks where response switches required additional executive control (see also Schulte et al. 2012). Greater medial frontal associative motor regional activation (SFG, SMA) to alcohol beverage pictures in CTL was related to this behavioral effort of response

inhibition, i.e., greater alcohol-cue effects (Diff. $RT_{alcpic-con}$) during response switching, whereas in ALC greater behavioral alcohol cue reactivity was related to the midbrain-limbic activation to alcohol cues and to higher alcohol craving scores. In addition, the greater midbrain-limbic response to alcohol pictures in ALC correlated with alcohol severity, i.e., higher amounts of lifetime alcohol consumption. Thus, even though ALC and controls did not differ in the their average behavioral performance, the within-group behavioral variance was related to their distinctive neural activation pattern, and in ALC with midbrain-limbic engagement and craving.

Similar to our previous finding (Müller-Oehring et al. 2013), we observed an overlap of the midbrain-limbic response to alcohol-related and emotion stimuli. This is not surprising considering that alcoholics with higher anxiety levels reported stronger alcohol craving prior to scanning and exhibited greater midbrain-limbic responses to angry face pictures during the scan. These findings support others linking mood to problematic alcohol consumption (Allan et al. 2015; Pedrelli et al. 2016) and to neural mechanisms supporting addictive behaviors (Durazzo et al. 2008; Gilman et al. 2008; Orban et al. 2008; Seo et al. 2011). On the other hand, we found fewer depressive symptoms in ALC who engaged midbrain limbic regions in response to happy face cues. It remains to be tested whether happy emotional faces could be used in stimulation approaches for operant conditioning of midbrain-limbic neural responsiveness during treatment to reduce depression in ALC (see e.g., Agyapong et al. 2015; Charlet et al. 2014). We further found greater cerebellar activation in ALC than controls for alcohol and emotion cue reactivity. Previous studies have identified a role for the cerebellum in reward and emotion processing (Stoodley and Schmahmann 2010) in drug (Moulton et al. 2014) and alcohol addiction (Fitzpatrick et al. 2008). Consistent with recent functional neuroimaging studies reporting greater cerebellar engagement by alcoholics who perform cognitive tasks at normal levels (Chanraud et al. 2011; Sullivan et al. 2013), our finding of enhanced cerebellar recruitment in response to affective cues could reflect a compensatory response tapping into corticolimbic regulatory systems (Stoodley and Schmahmann 2010). Nevertheless, the group-by-cue content interaction that indicated even less frontoparietal activation to alcohol beverage than angry face pictures in ALC, relative to controls, suggests that the engagement of cortical inhibitory mechanisms is particularly compromised in ALC when confronted with alcohol-related content. Consequently, we asked whether negative priming could help ALC to engage frontoparietal inhibitory control mechanism in the context of emotion and alcohol-related information.

As hypothesized, ALC did not activate midbrain-limbic areas with priming of an upcoming alcohol and emotion Stroop word conflict. Both groups now activated frontal executive control regions to primed alcohol-related and emotion Stroop processing. This finding suggests that neurofunctional systems in ALC can be primed to deal with upcoming emotion- and alcohol-related conflict and can overcome the prepotent midbrain-limbic cue reactivity response. In addition to the frontal cortical activation, ALC and controls in our study further activated the dorsal striatum to alcohol-related information, consistent with the role of the striatum in reward processing (e.g., Schott et al. 2008). The dorsal striatum has also been associated with habit formation (e.g., Smith and Graybiel 2016) and its heightened response to alcohol cues may mark a point in alcohol addiction when substance use has become habitual (see also Grüsser et al. 2004; Vollstädt-Klein et al. 2010). Here, ALC with

greater striatal activation had more severe alcoholism (AUDIT scores). Thus, the degree of the observed dorsal striatal activation to alcohol-related information may not only be a neural signature of processing the semantic 'alcohol' content in both groups (Duka and Townshend 2004; Lusher et al. 2004), but its heightened response in ALC may mark automatic, habitual drug seeking based on long-lasting stimulus–response associations (Ito et al. 2002) and thus index addiction severity (van Holst et al. 2014).

Behavioral responses were slowed in both groups when pictures primed the semantic content of the upcoming emotion and alcohol-related Stroop word (see Fig. 2); response times were also prolonged when compared to non-primed alcohol-emotion Stroop conflict processing (Table S2 in Supplement) (Müller-Oehring et al. 2013). This observation is consistent with semantic negative priming effect describing slower responses to an object that occurs subsequently to an ignored object (prime) of the same semantic category (Driver and Tipper 1989). In our priming Stroop task, it could be speculated that the prime (the picture of an alcoholic beverage or emotional face), which needed to be ignored during color-matching, led to active inhibition of its representation that spread through the semantic network to related concepts (e.g., alcohol and emotion Stroop words) (see e.g., Hutchison 2002). Today's understanding of negative semantic priming effects extends to more than one process and comprises next to attentional selection and inhibition, also episodic retrieval processes due to the sequential character of negative priming (for a review Frings et al. 2015). This behavioral priming effect was greater for alcohol-related than negative emotion context in both groups, which is consistent with other studies that used a modified alcohol Stroop paradigm and reported a strong attentional bias and distraction effect for alcohol-related stimuli in both heavy (Lusher et al. 2004) and social (Duka and Townshend 2004; Ryan 2002) drinkers.

With semantic priming, group differences were mainly observed in extrastriate cortices. Specifically, ALC showed less extrastriate activation than controls for primed alcohol-related Stroop processing but more extrastriate activation to positive emotion Stroop processing. Extrastriate cortices play a pivotal role in the selection of incoming information for further processing (King et al. 2012). Buschschulte and colleagues (Buschschulte et al. 2014) demonstrated this function in healthy subjects by showing that effective inhibitory control mechanisms can counter a selection bias for reward-associated features in extrastriate visual processing areas through interactions with prefrontal cortices. During abstinence (Fryer et al. 2013) and in treatment (Kamboj et al. 2011; Vollstädt-Klein et al. 2011), ALC can learn strategies to overcome their attentional bias to alcohol cues. Our results indicate that abstinent ALC may be able to withdraw attention from alcohol-related stimuli under priming conditions via extrastriate attentional selection mechanisms and to engage frontoparietal cognitive control systems (see also Luks et al. 2007). Accordingly, medial frontal activity correlated with smaller behavioral primed alcohol-Stroop effects and less alcohol craving in abstinent ALC.

The differentiated extrastriate response to primed alcohol and positive emotion Stroop in alcoholics (relative to controls) highlights the role of visual feature selection for processing (happy faces) or suppression (alcoholic beverages). Without priming ALC had shown failure to engage prefrontal cortices to positive emotion Stroop (Müller-Oehring et al. 2013) and it

could be speculated that happy face primes in the current study tuned prefrontal-extrastriate pathways towards attentional selection of positive information (see Troiani and Schultz 2013). It is possible that the observed cue reactivity and Stroop priming effects reflect neural mechanisms that are specific to sober ALC who have sought treatment during the course of their disease, but might be different in a non-treatment seeking sample. Further studies are needed to determine the clinical relevance of priming as a potential neuroprotective factor in relation to alcohol craving and relapse during the course of abstinence. Also the potential use of priming in treatment to prepare emotion and reward regulatory systems via stimulation techniques requires further work.

Group differences for primed negative emotional Stroop content occurred for subcortical areas, with ALC invoking left hippocampal and right pallidal areas more than controls and bilateral thalamic regions less than controls. Here, greater alcohol craving in ALC correlated with less thalamus and more hippocampal activity, emphasizing the role of limbic responsiveness to negative emotion for craving. Limbic structures including the hippocampus are key components in the emotion circuit that also regulate the reward circuit with its ventral striatal projections to the pallidum and midbrain (ventral tegmental area, substantia nigra) and back projections to the prefrontal cortex via the thalami nuclei (Haber and Knutson 2010). The different pattern of subcortical responsiveness of ALC and controls indicates aberrant regulation of the reward system via limbic structures for negative emotion.

Limitations of the present study arise from the non-alcohol drug use and tobacco smoking in almost 50 % of the ALC sample, which are common co-morbidities in individuals with alcoholism today. Although the preferred drug and most recent use was alcohol in these individuals, our findings of group differences on frontoparietal and midbrain-limbic network engagement may not be entirely specific to alcohol addiction and could apply to other addictive substances as well. Neutral pictures were not included in the task design because neutral subjective valence ratings can result from mixed feelings and any ambivalence in response to these pictures would undermine the experimental control (Schneider et al. 2016). Finally, as in all cross-sectional studies, causal inference cannot be made and our findings represent a snapshot in time of cue reactivity and primed alcohol-emotion conflict processing in sober alcoholics.

In summary, our findings indicate that neurofunctional systems in abstinent alcoholics can be primed to deal with upcoming emotion and alcohol-related conflict and to overcome the prepotent midbrain-limbic cue reactivity response.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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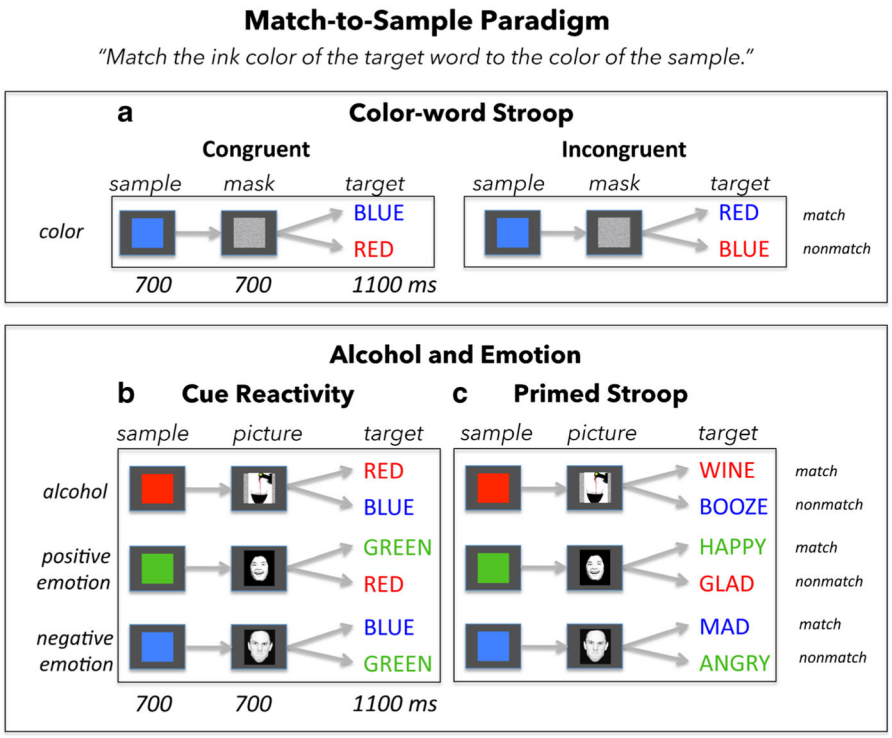

Fig. 1. Alcohol and Emotion Priming Stroop Match-to-Sample Paradigm

a *Color Stroop*: congruent (con) color-word (e.g., *RED* printed in red ink) (neutral condition) and incongruent (inc) color-word (e.g., *RED* printed in blue ink) (interference condition; Stroop conflict); **b** *Alcohol-emotion cue reactivity*: alcohol beverage (alcpic), happy (pospic) and angry face (negpic) pictures were presented between color samples and congruent color-word targets (no Stroop conflict); **c** *Primed alcohol-emotion Stroop*: the same alcohol beverage and emotional face pictures were given as in B, but now they were priming the alcohol-related (alc), positive (pos) and negative emotion (neg) word content of the upcoming Stroop target (Stroop conflict)

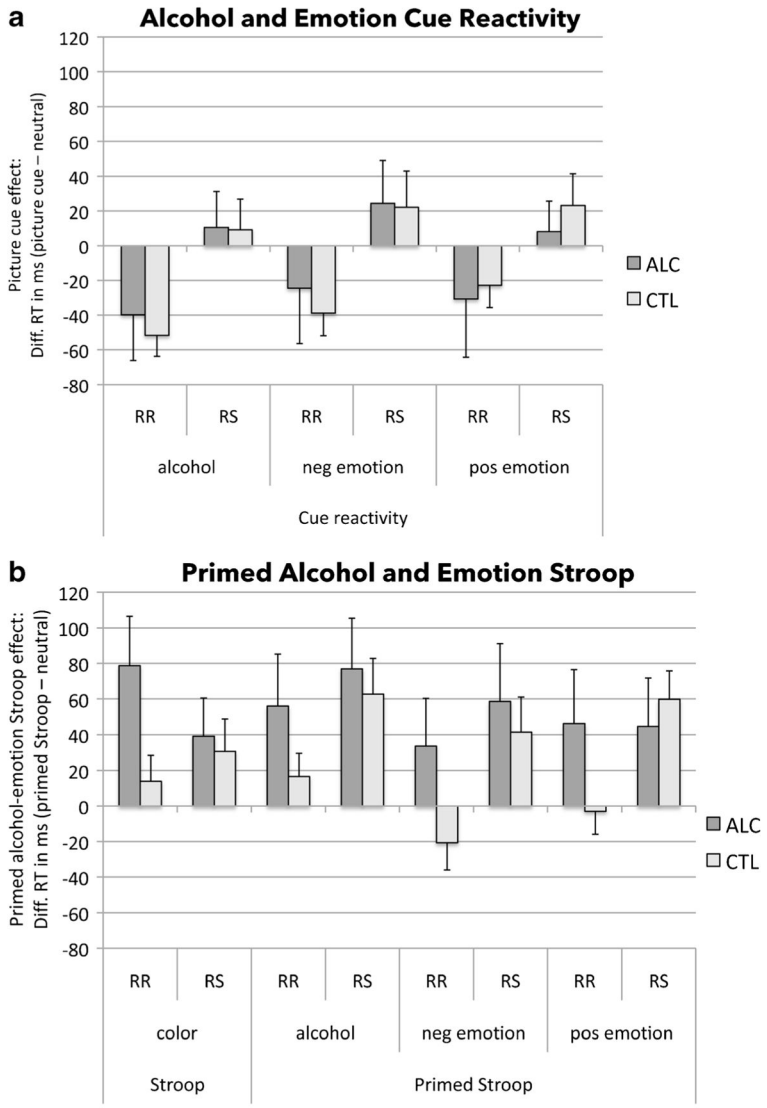

Fig. 2. Behavioral results

a *Cue reactivity effects*: Difference mean reaction times (RT) derived for alcohol beverage picture ($RT_{alcpic–con}$), happy face ($RT_{pospic–con}$) and angry face picture ($RT_{negpic–con}$) conditions, depicted for response repetition (RR) and response switching (RS) blocks. Positive difference RT values indicate response slowing, negative values reflect response facilitation. **b** *Primed Stroop effects*: Difference mean reaction time (diff. RT) derived for color (diff. $RT_{inc–con}$), primed alcohol (diff. $RT_{alc–con}$), positive (diff. $RT_{pos–con}$) and negative emotion (diff. $RT_{neg–con}$) Stroop conflict conditions; depicted for response repetition (RR) and response switching (RS) blocks. LEFT: Color Stroop effects (diff. $RT_{inc–con}$) are depicted for comparison with the alcohol and emotion Stroop conditions

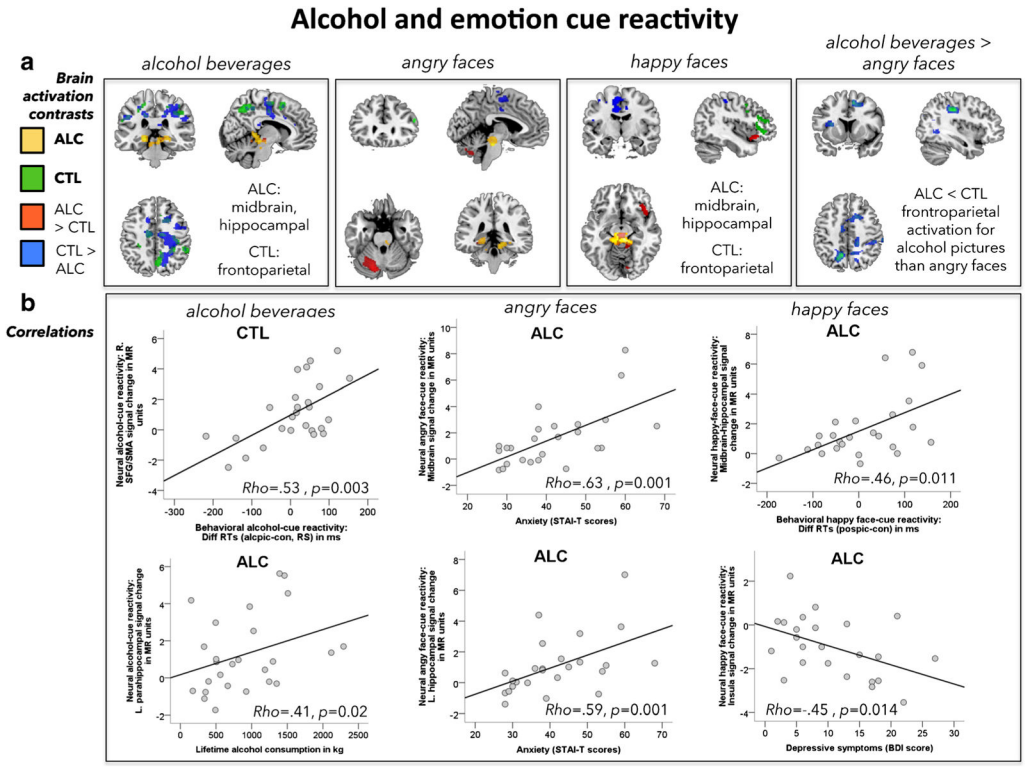

Fig. 3. Cue reactivity

a Brain activation contrasts for alcohol beverage (alcpic > con), happy face (pospic > con), and angry face (negpic > con) picture conditions in ALC and controls (CTL). **b** Brain-behavior correlation graphs

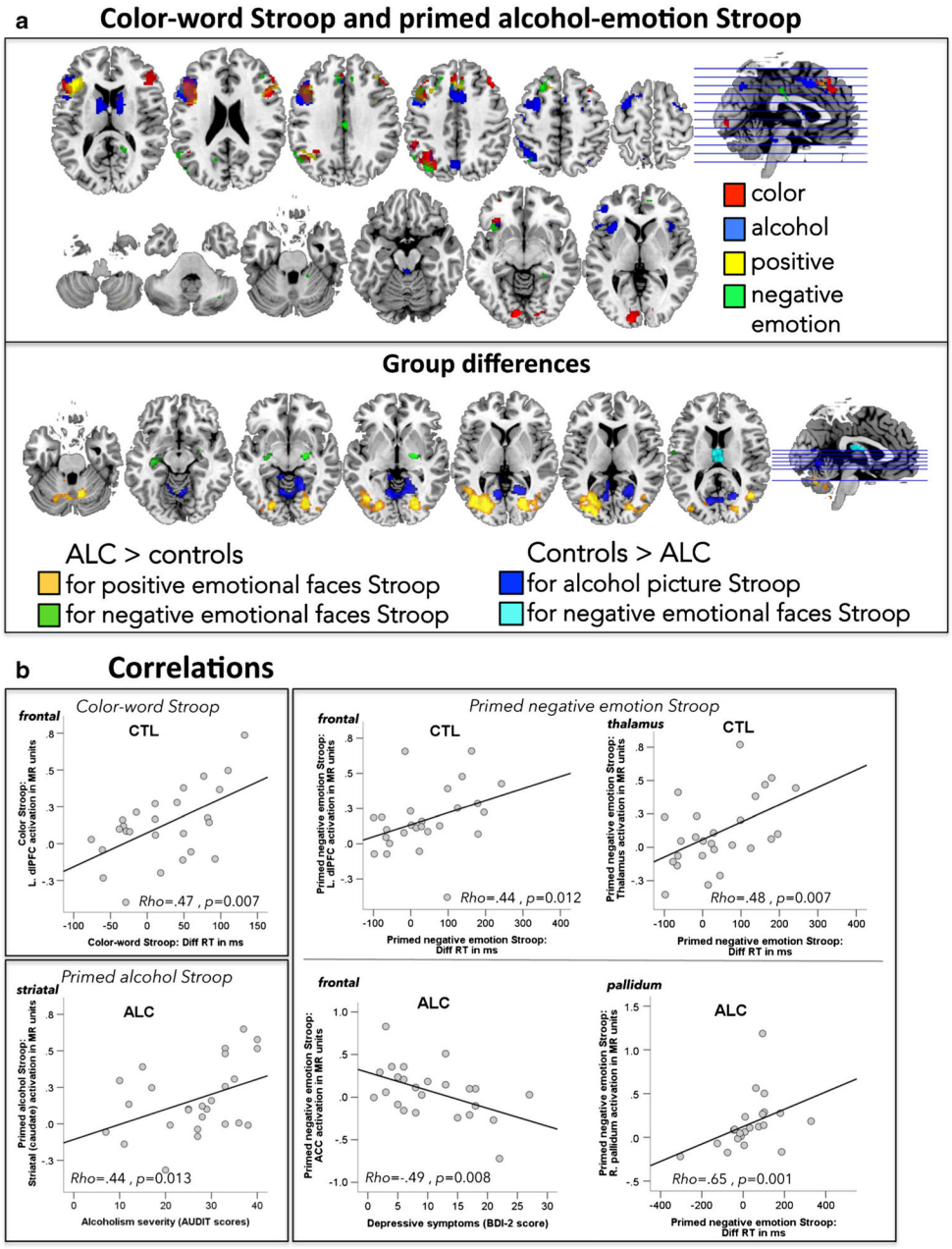

Fig. 4. Priming Alcohol-Emotion Stroop

a Brain activation patters for Stroop conditions over both groups (*UPPER PANEL*) and group activation differences for primed alcohol (alc > con) and emotion (pos > con; neg > con) Stroop processing (*LOWER PANEL*). **b** Brain-behavior correlation graphs

Table 1

Demographic characteristics of alcoholic (ALC) and control (CTL) study groups: Mean ± SD (range)

	ALC	CTL	*P* value
Women/Men	8/18	9/17	*n.s.*[a]
Age in years	49.9 ± 9.5 (26–65)	49.1 ± 11 (26–67)	*n.s.*
Handedness	24.7 ± 15 (14–70)	22.8 ± 11 (14–65)	*n.s.*
Education in years	13.7 ± 2.4 (8–18)	15.5 ± 2.4 (12–21)	*0.009*
Socioeconomic status	40 ± 10 (11–66)	29 ± 13 (11–54)	*0.004*
Verbal IQ (WTAR)	101 ± 12 (70–118)	107 ± 12 (77–119)	*n.s.*
Age at alcoholism onset in years	30 ± 13 (10–56)	-	
Duration of dependence in years	19.8 ± 10 (4–44)	-	
Lifetime alcohol consumption in kg	896.2 ± 568 (152–2291)	60.8 ± 93 (0–434)	*0.0001*
AUDIT total score	27 ± 10 (7–40)	2.5 ± 2.1 (0–10)	*0.0001*
Months abstinent (time since last drink)	3.87 ± 3.2 (0.2–12.3)	1.38 ± 3.4 (0.03–15.8)	*0.01*
Alcohol craving (ACQ-R) score	12 ± 7.9 (3.5–33)	7.8 ± 2.6 (0–13.5)	*0.012*
Depressive symptoms (BDI)	10.7 ± 7.2 (1–27)	2.7 ± 3.2 (0–10)	*0.0001*
Anxiety Scale (STAI)			
State anxiety	33.7 ± 10 (20–53)	27.6 ± 8.6 (20–50)	*0.028*
Trait anxiety	41.6 ± 11 (28–68)	30 ± 7.2 (21–45)	*0.0001*

[a]Chi square;

Abbreviations: Wechsler Test of Adult Reading (WTAR; (Wechsler 2001); ACQ-R, Alcohol Craving Questionnaire (Drobes and Thomas 1999; Raabe et al. 2005); Beck Depression Inventory (BDI-II; (Beck et al. 1996) depressive symptoms scores; State-Trait Anxiety Inventory (STAI; (Spielberger et al. 1983); Socioeconomic status (SES; (Hollingshead and Redlich 1958): lower values indicate higher SES; Handedness Inventory: scores 14–32 right-handed, 50–70 left-handed (Crovitz and Zener 1962)

Table 2

Neural Cue Reactivity to alcohol beverage and emotional face pictures for non-conflict (con) trials in alcoholics (ALC) and controls (CTL). 3dCusterSim calculation for multiple comparison correction at level $p < 0.05$ required a cluster size of $k = 197$ voxel in combination with a minimum *peak* threshold for each included voxel of $p = 0.005$

Region	BA	k extent	Z	MNI coordinates		
				x	y	z
Alcohol beverage pictures (alcpic > con)						
ALC: L. + R. midbrain, parahippocampal/hippocampus	27	755	4.05	−18	−34	−4
CTL: L. + R. medial frontal and middle cingulate gyri, supplementary motor area	6, 9, 31	1836	4.05	−12	−12	44
R. postcentral gyrus, inferior parietal lobe	2, 40	479	3.93	38	−26	40
R. precuneus	7	357	3.91	6	−56	50
L. precuneus, superior parietal lobe, postcentral	3, 7	442	3.79	−18	−46	56
L. medial frontal and anterior cingulate gyri	9, 24	174 [a]	3.22	−10	14	30
Happy face pictures (pospic > con)						
ALC: R. superior temporal gyrus, anterior insula	13, 38	250	4.56	46	16	−16
L. + R. midbrain, parahippocampal/hippocampus	27, 30	850	4.17	4	−24	−12
CTL: R. dlPFC	8, 9	641	3.75	22	40	26
L. medial frontal and middle cingulate gyri	6, 31	218	3.50	−12	−12	44
L. + R. precuneus	7	236	3.45	4	−64	44
Angry face pictures (negpic > con)						
ALC: R. posterior cerebellum		426	4.14	−16	−74	−26
L. + R. midbrain, R. parahippocampal/hippocampus	27, 35	564	3.99	−4	−24	−12
L. parahippocampal gyrus	35, 37	194	5.57	−20	−36	−8
CTL: R. dlPFC	46	109a	3.40	54	30	20

Abbreviations: BA brodmann area, *L* left, *R* right, parahippocampal = parahippcampal gyrus, *dlPFC* dorsolateral prefrontal cortex;

[a]subthreshold cluster size $k < 197$

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Table 3

Group Effect for Neural Cue Reactivity to alcohol beverage and emotional face pictures for non-conflict (con) trials (alcoholics = ALC, controls = CTL). 3dClustSim calculation for multiple comparison correction at level $p < 0.05$ required a cluster size of $k = 197$ voxel in combination with a minimum *peak* threshold for each voxel of $p = 0.005$;

Region	BA	k extent	Z	MNI coordinates		
				x	y	z
Alcohol beverage pictures (alcpic > con)						
ALC > CTL: L. + R. midbrain [1]		56	3.43	4	−22	−10
R. inferior frontal gyrus, anterior insula	47	73 [a]	3.63	44	20	−14
R. posterior cerebellum	18	143 [a]	3.61	12	−82	−16
CTL > ALC: L. + R. anterior and middle cingulate gyri	24, 31	2935	4.87	−8	14	30
R. middle cingulate and postcentral gryi	2, 24, 31	4600	4.82	14	−14	40
L. superior parietal and postcentral gyri	5, 6, 7	436	4.49	−18	−44	58
Angry face pictures (negpic > con)						
ALC > CTL: L. posterior cerebellum		964	4.47	−14	−74	−28
L. + R. midbrain [1]		189	3.20	4	−22	−2
R. anterior cerebellum		151 [a]	3.48	32	−56	−28
CTL > ALC: L + R medial frontal cortex, SMA	6	191 [a]	3.70	−6	−6	58
L. anterior cingulate cortex (ACC)	32	128 [a]	3.79	−8	16	28
R. precentral gyrus	6	121 [a]	3.23	8	−20	70
Positive face pictures (pospic > con)						
ALC > CTL: L. posterior cerebellum		237	4.09	−14	−76	−28
L. + R. midbrain [1]		92	3.45	2	−22	−12
R. posterior cerebellum		123 [a]	3.60	16	−78	−24
R. anterior insula, inferior frontal gyrus	13, 47	102 [a]	3.55	44	22	−14
CTL > ALC: L + R medial frontal and anterior cingulate gyri	6, 24	3642	4.67	−8	14	30
L. superior temporal, inferior parietal lobe	22, 40	413	3.94	−58	−38	20
R. dlPFC, anterior cingulate gyrus	9, 32	403	3.82	24	38	28
L. pre- and postcentral gyri	3, 6, 43	450	3.50	−50	−6	18
R. middle frontal, precentral gyri	6, 8	441	3.44	24	16	42

Region	BA	k extent	Z	MNI coordinates x	y	z
L. middle cingulate and paracentral gyri, precuneus	5, 7, 31	275	3.22	−18	−32	38
Interaction: angry faces > alcohol beverages (negpic > con) > (alcpic > con)						
CTL > ALC: L. superior parietal lobe, precuneus	7	716	4.28	−16	−62	58
R. inferior parietal lobe, precuneus	7, 40	1038	4.25	38	−30	40
R. cingulate gyrus, precuneus	7, 31	294	3.93	16	−34	42
L. inferior parietal lobe, supramarginal gyrus	40	544	3.81	−48	−36	32
L. cuneus, middle temporal gyrus	18, 39	398	3.77	−22	−68	14
R. superior and medial frontal, cingulate gyri	6, 24	299	3.47	10	12	52
R. posterior cingulate gyrus, cuneus	18, 31	292	3.43	12	−56	20
L. fusiform, middle occipital, parahippocampal gyri	19	465	3.40	−36	−64	−6
L. middle cingulate gyrus	24, 31	310	3.42	−14	−30	34
R. lingual, middle temporal, parahippocampal gyri	18, 19, 37	622	3.29	26	−78	−2
L. anterior insula	13	274	3.28	−32	14	12

Abbreviations: BA brodmann area, *L* left, *R* right, *SMA* supplementary motor area, *dlPFC* dorsolateral prefrontal cortex;

[a]subthreshold cluster size $k < 197$

[1]small volume $p_{FWE\text{-}corrected} < 0.05$

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Table 4

Stroop conflict-related brain activation to A. Stroop interference from incongruent (vs. congruent) color words, and from alcohol, negative and positive emotion words with picture priming; B. Group differences between alcoholics (ALC) and controls (CTL); 3dClusterSim calculation for multiple comparison correction at level $p < 0.05$ required a cluster of $k = 197$ voxel ($p_{peak} = 0.005$);

Region	BA	k extent	Z	MNI coordinates		
				x	y	z
A. Stroop conditions						
Color Stroop (inc > con)						
L. dorsolateral prefrontal cortex (dlPFC), inferior and middle frontal gyri	9, 46	1265	4.79	−46	18	24
R. dlPFC, inferior and middle frontal gyri	8, 9	535	4.58	40	24	48
L. lingual and fusiform gyri, cuneus	17, 18, 37	342	4.44	−6	−90	−6
L. superior and inferior parietal, supramarginal gyri	7, 40	769	4.35	−36	−64	48
L. + R. medial frontal gyrus	8	176 [a]	3.96	−2	32	48
Alcohol Stroop with alcohol picture priming (alc > con)						
L. dlPFC, inferior and middle frontal gyri	9, 45, 46	2052	5.91	−48	8	38
L. + R. medial frontal gyrus/premotor cortex, middle and anterior cingulate gyri	6, 9, 32	511	4.96	4	8	44
R. caudate nucleus		301	4.05	12	4	14
L. superior and inferior parietal lobe	7, 40	595	4.05	−32	−60	46
L. caudate nucleus		295	3.99	−10	0	12
L. anterior insula, inferior frontal gyrus	13, 47	229	3.95	−32	20	2
Positive-Emotion Stroop with happy face priming (pos > con)						
L. dlPFC, inferior and middle frontal gyri	9, 45, 46	1250	4.81	−42	24	16
L. + R. medial frontal gyrus/premotor cortex	6, 8	204	3.99	−4	28	48
R. dlPFC	9, 46	171 [a]	3.55	58	24	24
L. superior parietal lobe, angular gyrus	7, 39	191 [a]	3.29	−30	−68	46
Negative-Emotion Stroop with angry face priming (neg > con)						
L. dlPFC, middle frontal gyrus	8, 9	709	4.62	−46	14	40
L. medial frontal and middle cingulate gyri	8, 32	414	4.35	−22	24	52
L. superior parietal lobe	7	492	3.91	−34	−70	46
B. Group differences						
Alcohol Stroop with alcohol picture priming (alc > con)						

Region	BA	k extent	Z	MNI coordinates x	y	z
CTL > ALC: L. + R. cuneus, lingual gyrus, cerebellum	18, 19	1009	4.00	−8	−62	−2
Positive-Emotion Stroop with happy face priming (pos > con)						
ALC > CTL: R. lingual, cuneus	17, 18	380	4.05	22	−74	0
L. posterior cingulate middle occipital gyri	19, 30	960	3.63	−40	−70	4
L. + R. posterior cerebellum		267	3.44	14	−64	−28
Negative-Emotion Stroop with angry face priming (neg > con)						
ALC > CTL: R. globus pallidus[1]		84	3.71	22	−12	−4
L. hippocampus[1]		49	2.92	−34	−20	−12
CTL > ALC: L. + R. thalamus[1]		177	3.85	2	−18	18

Abbreviations: BA brodmann area, *L* left, *R* right, *dlPFC* dorsolateral prefrontal cortex;

[a]subthreshold cluster size $k < 197$

[1]small volume $p_{FWE\text{-}corrected} < 0.05$