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Extended-release naltrexone (XR-NTX) attenuates brain responses to alcohol cues in alcohol-dependent volunteers: A bold FMRI study

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ABSTRACT

Oral naltrexone reduces heavy drinking, but is less consistent as an abstinence promoter, whereas once-monthly extended-release naltrexone (XR-NTX) also maintains abstinence. The present study sought to determine if alcohol cue reactivity is attenuated by XR-NTX. Twenty-eight detoxified alcohol-dependent adult male and female volunteers received a single i.m. injection of either XR-NTX or placebo under double-blind conditions. An fMRI/cue reactivity procedure was conducted immediately before and two weeks after injection. At baseline, alcohol-related visual and olfactory cues elicited significant increases in orbital and cingulate gyri, inferior frontal and middle frontal gyri. Subsequently, brain activation was significantly altered in XR-NTX-treated individuals. These affected brain regions are associated with the integration of emotion, cognition, reward, punishment, and learning/memory, suggesting that XR-NTX attenuates the salience of alcohol-related cues. Such an effect on brain function may interrupt the processes associated with "slips" and relapse, which may account for XR-NTX's ability to maintain abstinence.

Introduction

Oral naltrexone has a long record of safe clinical use in the treatment of opioid addiction and alcohol dependence. This drug exhibits a low level of toxicity, and in clinical use, adverse events (AEs) are generally mild or moderate and reversible (McEvoy, 1999). In addition, when combined with various treatment programs, naltrexone has been found to decrease drinking rates, prolong abstinence, and hinder relapse to uncontrolled drinking among abstinent alcoholics who sampled alcohol during treatment (Anton, 1999; Kranzler, 2000; O'Malley et al., 1992; Volpicelli et al., 1992). However, shortcomings related to compliance and adverse effects limit the utility of oral naltrexone for the treatment of alcohol dependence. Meta-analyses of placebo-controlled trials of oral naltrexone (n = 19), have failed to find significant benefit for complete abstinence rates during treatment (Bouza et al., 2004; Srisurapanont and Jarusuraisin, 2005) and some have raised the possibility that naltrexone's benefit may even require "sampling" alcohol in order to facilitate extinction (Sinclair, 2001).

In April 2006, Vivitrol® (naltrexone for extended-release injectable suspension or XR-NTX) was approved in the United States for the treatment of alcohol dependence in subjects who are able to abstain from alcohol in an outpatient setting prior to initiation of treatment (Gastfriend, 2011). This extended-release, microsphere formulation of naltrexone is administered by intramuscular (IM) gluteal injection every 4 weeks and in abstinent alcohol dependent adults receiving psychosocial therapy, has demonstrated efficacy in prolonging initial abstinence and maintaining total (i.e., 6-month) abstinence compared to placebo — i.e., in the absence of "sampling" alcohol (O'Malley et al., 2007). XR-NTX is generally well tolerated and only infrequent treatment-related AEs have been reported (nausea, injection site reaction and headache). This raises the question as to what is the mechanism by which XR-NTX might exert its clinical effect on abstinence.

It has been suggested that exposure to cues may lead to the activation of certain "automatic" cognitive functions, resulting in repetitive, unwanted thoughts about alcohol. These automatic thoughts are the cognitive equivalent of unconscious craving (Anton, 2000). Craving also may arise in part from persistent nervous system changes (i.e., neuroadaptation) that leave the alcoholic's brain vulnerable to relapse drinking (Koob, 2000). These changes persist in the absence of alcohol, and may result in conscious or unconscious physical and mental distress. This phenomenon could account for the craving alcoholics experience soon after the cessation of drinking, which makes them vulnerable to relapse for a protracted period of time.

A comprehensive understanding of craving requires the integration of unconscious and cognitive mechanisms (Rohsenow and Monti, 1999). Among the concepts of craving discussed here, both the social learning and cognitive processing models implicate cognitive learning in the development of harmful drinking patterns and

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stress the importance of teaching conscious coping strategies in alcoholism therapy. Both of these models are also consistent with the involvement of other causal mechanisms, including reinforcement and other unconscious processes (Anton, 1999; Tiffany, 1999).

Craving studies based on a wide-range of imaging technologies of humans have identified specific regional changes in brain cell activity in response to alcohol-related cues (Anton et al., 2001; George et al., 2001; Hommer, 1999). Because these findings alone do not prove that the observed brain changes actually *cause* the subjective sensation of craving (Sayette et al., 2000), a more precise method to monitor how these urges affect the brain and is needed, and fMRI is well suited to provide this metric.

Echo-planar fMRI increases the temporal resolution for acquiring functional neuroanatomical images beyond what has been available with radionuclide scanning. Compared to other imaging modalities, fMRI is more likely to identify transient drug-induced changes in regional cerebral blood flow (CBF) or metabolism. Spatial resolution is excellent with fMRI, which contains connectivity and functional information in the same image.

The use of fMRI to track the effects of alcohol-related stimuli on central nervous system function has been well-validated. Braus et al. (2001) demonstrated that the ventral striatum (VS) was activated by presenting recently detoxified alcoholics with alcohol-associated visual cues. This research team later showed that this cue activation in the striatum and medial prefrontal cortex was associated with subsequent relapse in abstinent alcoholics (Grusser et al., 2004), while Kareken et al. (2004) demonstrated that olfactory cues activated nucleus accumbens and ventral tegmental areas in high risk drinkers. Finally, Myrick et al. (2008) demonstrated that oral naltrexone alone, and in combination with ondansetron, decreased alcohol cue-related activation of the VS in alcohol-dependent individuals. Only visual cues were studied and the analyses were confined to the VS.

Here, we tested the ability of a single i.m. injection of XR-NTX to alter whole-brain activation patterns (as measured by BOLD fMRI) associated with the delivery of alcohol-related visual and olfactory cues in individuals who are being treated for their alcohol dependence.

Methods

General

The present study was a double-blind, placebo-controlled between-subject design to test whether XR-NTX attenuates brain responses to alcohol-related olfactory and visual cues in treatment-seeking alcohol-dependent individuals. The protocol was reviewed and approved by the McLean Hospital Institutional Review Board (IRB); all participants read and signed an informed consent form before receiving a physical exam and psychiatric screen to participate in the study. A total of 31 adult (age 46.6 ± 9.2 years, mean ± S.D.) male (N = 21) and female (N = 10), recently detoxified individuals passed the screening protocol and were randomized to the protocol. Medication randomization was stratified by sex and age. A total of 24 were Caucasian and 7 were African American. The participants reported drinking on average a total of 82.8 ± 10.8 drinks per week during their most recent drinking period prior to their detoxification. A separate drug use questionnaire was used to collect information of drug and alcohol use histories and patterns. Mean age of initiation of heavy drinking was reported to be 24.7 ± 10.8 years (range 16–55). Nineteen did not smoke tobacco and those who did smoke reported smoking 17.3 ± 7.4 cigarettes per day. Thirteen reported using no other drug of abuse, while the remainder reported occasional (or past) use of cannabis (N = 11), cocaine (N = 10) and opioids (N = 1); some participants reported using more than one drug. All received a diagnosis of alcohol dependence via DSM-IV criteria and none received a diagnosis of dependence on any other drug including opiates, stimulants or sedative/hypnotics.

Medication treatment

The fMRI results are based on 28 individuals who successfully completed both fMRI sessions, yielding valid pre and post treatment data. Of these 28 participants, a total of 15 were randomized to receive XR-NTX (380 mg, i.m.), while 13 received placebo injection. XR-NTX is a microsphere formulation of naltrexone for suspension that is available in dose strength of 380 mg naltrexone per vial. The XR-NTX microspheres contain approximately 34% (w/w) naltrexone incorporated into a 75:25 matrix of poly (*D,L*-lactide co-glycolide) polymer (PLG). PLG is a common, biodegradable medical polymer having a history of safe human usage in sutures, bone plates and slow-release pharmaceuticals (e.g., Risperdal Consta®, Zoladex®, Lupron Depot®, Decapeptyl® SR and Sandostatin LAR® Depot). Placebo for XR-NTX microspheres consists of a sterile, white, powder of 75:25 PLG.

Behavioral treatment

All participants attended weekly relapse prevention counseling sessions conducted by a trained clinician—this was done to ensure that placebo-treated participants received some form of therapy. The sessions lasted approximately 60 min. A cognitive strategy was used with an emphasis on self-management and coping skills. The goal of the treatment was to develop coping skills that would help the participants maintain abstinence from alcohol. A Clinical Global Impressions (CGI) was also performed at each study visit to assess therapeutic effect.

The day after the fMRI scan (Day 1), subjects were contacted via telephone by site personnel to offer support following cue exposure. In addition, weekly visits were conducted for the first month after dosing and included the following assessments: laboratory tests, adverse events (AEs), vital signs, questionnaire responses and urine toxicology. Pregnancy tests were conducted as applicable on a monthly basis.

Experimental procedure

Data were acquired using a Siemens 3 T Trio whole body scanner with a transmit-receive quadrature birdcage head coil. A baseline fMRI scan/cue reactivity assessment was conducted at Visit 2 (Day 0) prior to randomization. Subject responses were collected via a keypad device in response to a computerized visual analog questionnaire. Visual stimuli were delivered using a projector, translucent screen, and mirrors; a custom-built olfactometer based on Lowen and Lukas (2006) provided olfactory stimuli. See Fig. 1 for a layout of the room configuration. The participants were instructed to use a MR compatible, fiber optic response pad (FORP, Current Designs, Inc., Philadelphia, PA) to move the cursor on the screen. An identical procedure was performed two weeks later.

Olfactory/visual cues

The MR-compatible olfactometer device (Lowen and Lukas, 2006) delivered one of the three odorants [alcohol, phenyl ethyl alcohol (rose scent) and humidified air (no odor)] automatically via computer control through a disposable nasal cannula. The three odorant streams converged near the subject to minimize delay due to dead space. Participants were exposed to their *preferred* brand of alcohol. For those who preferred beer, a thin layer of canola oil (1 mL) was floated on this odorant to retard foaming. Pictures of alcohol- and non alcohol-related images were presented to the participants via the translucent screen. The alcohol-related images depicted various types of beer, wine and distilled spirits in standard glasses and/or bottles while the non-alcohol images were photos of water, milk and tea in their various containers. Fig. 2 depicts the experimental procedure. All participants viewed the same series of images, regardless of their preferred alcoholic beverage.

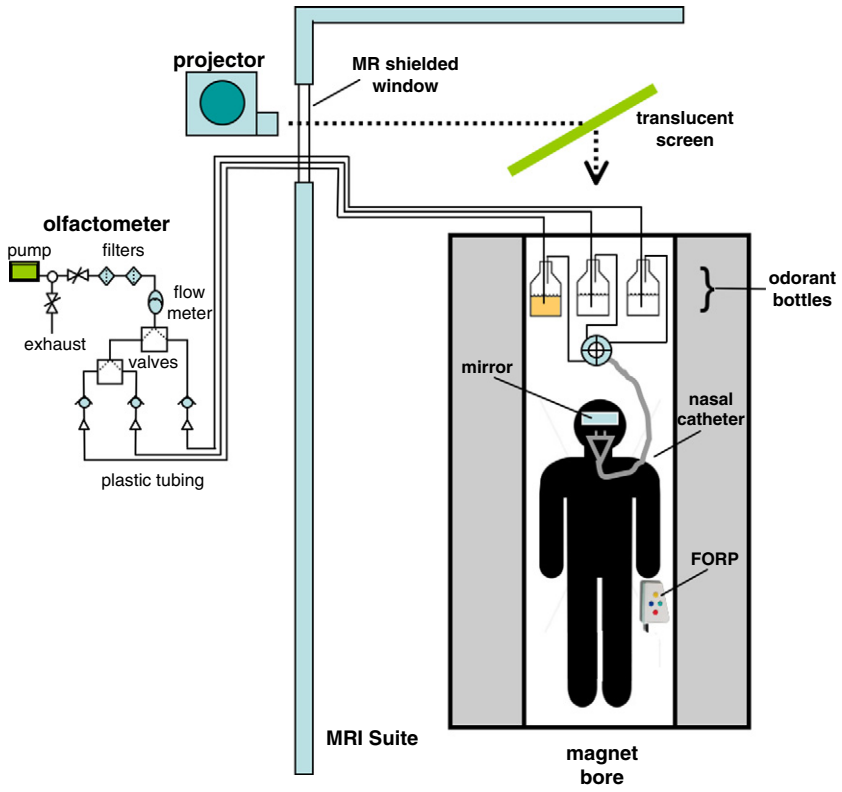

Fig. 1. Bird's eye view of the 3 T magnet scanner suite. Visual stimuli and VAS scales are projected onto a translucent screen that the participant can see with the aid of a small mirror that is fixed at a 45° angle. Participants' score responses using the FORP device. An olfactometer device is used to deliver olfactory cues. The air supply and switching mechanisms are located outside of the imaging suite, but the odorant bottles are located just inside of the bore about 1.5 m from the participant's head.

Presentation of the stimuli

Functional scanning comprised a single, 28-min BOLD scan, divided into 1-min blocks. Each block began with two Likert questions ("Want to drink alcohol" and "Want to avoid drinking alcohol"), at 6 s each. Each question began with the response indicator blank; the first key press made the indicator appear in the middle of the scale. This provided an indicator for a lack of response. Subjects were able to complete these questions within the time allotted. A final question pair was presented after the end of the last block. Pictures were presented during the remaining 48 s of the block consisting of either

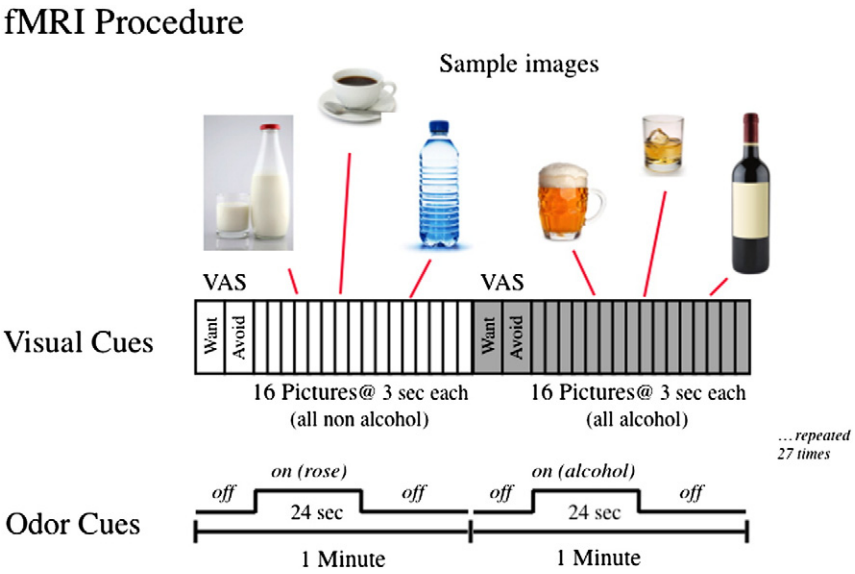

Fig. 2. Experimental protocol—cue presentation during fMRI recording. Each minute of the scanning sequence was composed of one set of pictures – either alcoholic or non-alcoholic, and one odor – either rose or alcohol. Therefore, there were 4 conditions: alcohol pictures with and without alcohol odors, and non-alcoholic pictures with and without alcohol odors. Two VAS questions were asked at the beginning of each sequence: "Want to drink alcohol", and "Want to avoid drinking alcohol?" Subjects had 6 s to answer each question. Air (pumped through water without any odor) flowed while they were answering these questions and air again after the odor was turned off. After answering the questions, no other response was required. The order of presenting non-alcohol versus alcohol-related images was counterbalanced—in this example of two sequences the non-alcohol images are presented first (only a sample of the images is presented) and the rose odor was presented first followed by the alcohol odor; two additional sequences are presented with the odors reversed.

alcohol or placebo, the same type for the entire block. An odor, either alcohol or placebo, was turned on at the beginning of the picture presentation, and turned off 24 s later (to prevent habituation effects). All four odor/picture combinations were presented in a counterbalanced design identical for all subjects, with the same odor or picture type never appearing more than two blocks in a row. Both immediately before and immediately after the BOLD scan, subjects completed an AAAQ (McEvoy et al., 2004) using a Likert scale. The scale started at "Not at all" for all questions except for the "Aroused" question that began in the middle. Subjects moved the indicator using the FORP device, and had 10 s to respond to each of the 18 questions.

fMRI scanning

Scans were performed on a 3 T Siemens Trio MR imaging system (Siemens AG, Erlangen, Germany). The BOLD scan was a gradient echo EPI, TR/TE = 3000/30 ms, 224 × 224 mm FOV, 41 3.5-mm interleaved axial slices starting from the spinal cord covering the entire brain, no gap, AP readout, 64 × 64 pixel, full k-space acquisition, no SENSE acceleration; pulse sequence-enhanced version of the Siemens epibold, yielding isotropic 3.5 mm voxels. The BOLD scan comprised 567 acquired images, preceded by two additional images (6 s) to ensure steady-state magnetization. Other scans included a T1-weighted matched-warped scan (Rohan et al., 2001), and a standard T1 weighted MP-RAGE3D scan (FOV = 256 × 256 × 170 mm, 256 × 256 × 128).

fMRI analysis

With the exception of a few in-house programs, data processing was performed using FSL Release 4.1.2 (FMRIB Analysis Group, Oxford University, UK, http://www.fmrib.ox.ac.uk/fsl/), specifically FEAT version number 5.98, set to default values unless otherwise specified. An in-house despiking filter was applied to all BOLD data first. Subsequent preprocessing steps were motion correction using mcflirt (Jenkinson et al., 2002). If the maximum Euclidean deviation from this reference exceeded 3.5 mm (the voxel dimension) for an image, that image was effectively removed from analysis (see "Single-image regressors", below). If more than ten such images occurred in any scan, both scans (all MRI data) for that subject were discarded. Slice timing correction was performed and all non-brain voxels were removed. Spatial filtering was then performed, followed by global normalization and temporal high-pass filtering with a cutoff of 120 s. Regularized autocorrelation functions were independently estimated for each voxel, using temporal Tukey prewhitening (Woolrich et al., 2001). Regressors comprised the following: one for each of the two picture types; one for each of the two odor types, matching the odor response temporal profile (a trapezoidal form defined by convolving the 24-s odorant presentation time with a rectangular pulse with duration equal to a typical breathing cycle of ten breaths per minute); habituation terms for these four regressors, generated by multiplying each regressor by a linear ramp and then orthogonalizing this against the original regressor; an odor-by-picture interaction term; six motion regressors; and single-image regressors, one for each image for which the deviation exceeded 3.5 mm.

Each odor, picture and interaction regressor was subjected to a linear filter modeling the hemodynamic response function, having a gamma impulse response, width of 3 s, and mean lag of 6 s. These regressors were further subjected to the same temporal filter that was applied to the data. The results of this analysis were discarded except for the residuals. A principal component analysis was performed on the 5000 voxels in the residuals that had the largest variance (Madsen and Lund, 2006). The first eight components were retained and used as additional nuisance regressors (without hemodynamic or other temporal filtering) in a new general linear model, using the same pre-processed functional data. Contrasts examined were as follows: control odor minus alcohol odor, control pictures minus alcohol pictures, the two corresponding habituation terms, and the interaction, as well as the opposites (negatives) of these.

Functional results were aligned with the matched T1-weighted scan, which was in turn aligned with the high-resolution MPRAGE scan and then the MNI152 standard brain using FNIRT. Rendering of the functional results in MNI space was performed once, after concatenating the three alignments into a single matrix. A summary of this registration was monitored for each run of each subject; no runs were eliminated due to registration failure. Contrasts were compared between the two scan visits (pre- and post-administration) in a fixed effects model. These single-subject results were combined in a mixed effects model, and group contrasts run for the differences between the two groups (XR-NTX and placebo). All results were first converted to Z-scores, and thresholded to a significance level of $p < 0.01$ (uncorrected). Using Gaussian random field theory, clusters were found that achieved a cluster-wide significance level of $p < 0.05$, FWE corrected for multiple comparisons over the whole brain.

Results

Demographics and Subjective reports of alcohol effects

The demographic profile of the two treatment groups is shown in Table 1. Participants were in their mid 40's to early 50's year of age with similar levels of education, drinking history and number of days sober before entering the study. There were no significant differences between the two treatment groups among any of the measures at the baseline phase of the study. While the duration of abstinence was quite variable, the present study was not powered to test whether this factor contributes to the effects of XR-NTX on cue reactivity.

Table 1
Demographic profile of alcohol-dependent individuals who received one injection of either XR-NTX or placebo. T-test for continuous variables, Chi-squared for discrete variables, both two-tailed.

Demographics	XR-NTX	Placebo	T-test
Mean ± sd	(N = 15)	(N = 13)	*p* value
Age (yrs)	49.93 ± 6.22	46.54 ± 8.52	$p = 0.235$
Males # (%)	11 (73)	10 (77)	
Caucasian # (%)	12 (80)	10 (77)	
Education (years)	14.43 ± 1.90	14.00 ± 1.78	$p = 0.541$
Height (cm)	173.06 ± 11.59	174.09 ± 8.14	$p = 0.791$
Weight (kg)	88.18 ± 17.14	81.65 ± 16.27	$p = 0.313$
BMI (kg/m^2)	29.31 ± 4.04	26.71 ± 3.44	$p = 0.081$
Age drink heavily (yrs)	27.36 ± 12.53	22.67 ± 8.99	$p = 0.291$
No. drinks/wk (most recent)	92.38 ± 67.17	75.03 ± 55.61	$p = 0.468$
Days sober @ baseline	42.40 ± 31.53	59.85 ± 65.14	$p = 0.365$

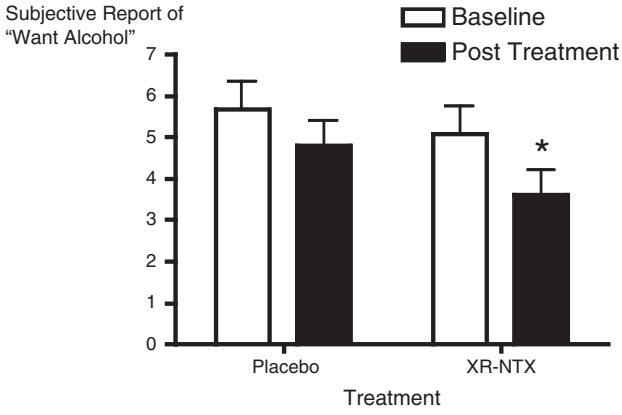

Fig. 3. Peak reports of "Want Alcohol" during the fMRI session during which participants were exposed to both olfactory and visual cues. * indicates significant difference from baseline.

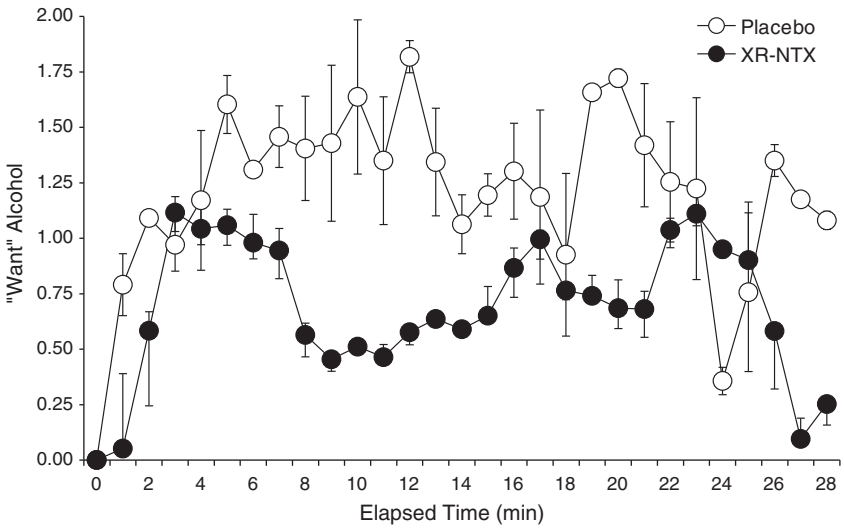

Fig. 4. Time course of reports of "Want Alcohol" during the fMRI session, during which participants were exposed to both olfactory and visual cues.

Fig. 3 shows the changes in subjective reports of "Want Alcohol" during the MRI procedure at both baseline and again two weeks after XR-NTX or Placebo injection. During the scans, the participants were exposed to both olfactory and visual cues during a 28-min session while they responded to a visual analog scale on how much they wanted alcohol *at that time*. The results of a 2×2 ANOVA revealed that XR-NTX caused a significant reduction in reports of "want" alcohol while placebo had no effect on desire for alcohol. The time course of the changes in "want" alcohol during the second cue presentation/fMRI session are shown in Fig. 4. Both placebo- and XR-NTX-treated individuals experienced an initial increase in reports of "want" as the session started, but the XR-NTX treated group experienced a reduction in desire for alcohol about 8–10 min after session onset. Desire for alcohol rose again toward the end of the session, but remained lower than that reported by the placebo-treated group.

fMRI

The fMRI results are described in terms of baseline effects of the cues, followed by the effect of treatment on the BOLD signal activation pattern to these cues at week 2 after treatment. During baseline, alcohol-related visual and olfactory cues elicited significant changes in multiple brain regions that were distinctly different from one another (Fig. 5 and Table 2). Both BOLD signal deactivation and

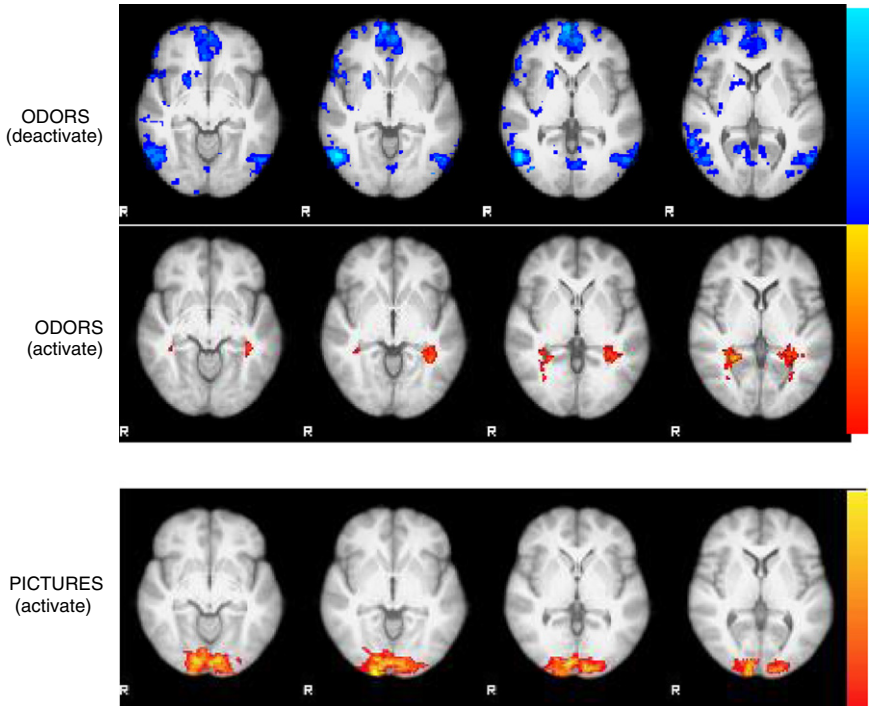

Fig. 5. Changes in BOLD signal activation in response to alcohol-related and non-alcohol related odors and pictures during the baseline scan. Top row (odors-deactivation): non alcohol > alcohol contrasts; middle row (odors-activation): alcohol > non alcohol odor contrasts. Bottom row (pictures-activation): alcohol > non-alcohol picture contrasts. Z-score range for odors is 2.3–5.0 and Z-score range for pictures is 2.0–5.8.

Table 2
Standard space coordinates, cluster size and significance of contrast to each condition.

Cluster	Activation extrema (region)	MNI x	MNI y	MNI z	Extent (mm^3)	Z	Other regions
Odor response-deactivation (Fig. 5, top)							
1	R. Lateral occipital cortex, inferior division	52	−66	0	181,168	5.04	R. Lateral occipital cortex, superior division
	R. Frontal pole	4	64	−2		4.58	R. Precuneous cortex
	R. Middle temporal gyrus, temporooccipital part	58	−52	8		4.52	R. Paracingulate gyrus
	R. Cingulate gyrus, anterior division	6	12	42		4.43	L. Lateral occipital cortex, inferior division
	R. Middle temporal gyrus, temporooccipital part	62	−58	10		4.38	L. Lateral occipital cortex, superior division
	R. Precuneus cortex	4	−74	66		4.25	R. Cingulate gyrus, posterior division
2	R. Frontal pole	40	44	30	47,112	4.8	L. Precuneous cortex
	R. Middle frontal gyrus	50	8	44		4.77	L. Paracingulate gyrus
	R. Frontal pole	28	46	34		4.69	L. Cingulate gyrus, anterior division
	R. Frontal pole	28	38	40		4.69	R. Inferior temporal gyrus, temporooccipital part
	R. Superior frontal gyrus	28	6	58		4.58	L. Cingulate gyrus, posterior divisio
	R. Frontal pole	42	38	32		4.44	R. Supramarginal gyrus, posterior division
3	L. Frontal pole	−38	46	30	14,472	4.4	R. Angular gyrus
	L. Frontal pole	−32	52	30		4.28	R. Juxtapositional lobule cortex
	L. Frontal pole	−34	56	20		4.17	R. Supramarginal gyrus, anterior division
	L. Middle frontal gyrus	−42	34	36		4.11	R. Frontal medial cortex
	L. Frontal pole	−34	40	40		4.1	L. Lingual gyrus
	L. Frontal pole	−26	50	34		3.86	R. Lingual gyrus
4	L. Precentral gyrus	−40	−2	56	6184	3.9	R. Postcentral gyrus
	L. Precentral gyrus	−36	−4	52		3.83	R. Superior parietal lobule
	L. Superior frontal gyrus	−22	4	66		3.8	R. Cuneal cortex
	L. Postcentral gyrus	−54	−10	30		3.76	R. Middle temporal gyrus, posterior division
	L. Precentral gyrus	−32	−8	46		3.73	L. Inferior temporal gyrus, temporooccipital part
	L. Precentral gyrus	−50	−8	28		3.55	R. Inferior frontal gyrus, pars triangularis
							R. Temporal occipital fusiform cortex
							R. Frontal orbital cortex
							R. Superior temporal gyrus, posterior division
							R. Inferior Frontal gyrus, pars opercularis
							L. Frontal medial cortex
							L. Intracalcarine cortex
							R. Planum temporale
							L. Middle temporal gyrus, temporooccipital part
							R. Temporal pole
							R. R. occipital pole
							R. Subcallosal cortex
Odor response-activation (Fig. 5, middle)							
1	R. Lingual gyrus	28	−48	4	13,768	4.28	L. Hippocampus
	—	32	−46	6		4.11	
	—	−16	−40	14		3.88	
	L. White matter	−38	−48	−4		3.75	
	L. White matter	−20	−52	12		3.74	
	R. White matter	26	−50	18		3.71	
2	L. White matter	−24	−10	28	3256	3.58	
	L. White matter	−24	8	28		3.44	
	L. White matter	−26	−16	30		3.36	
	L. White matter	−24	−4	28		3.2	
	L. White matter	−36	−16	24		3.19	
	L. White matter	−20	8	20		3.05	
Picture response-activation (Fig. 5, bottom)							
1	L. Occipital pole	−4	−94	−10	31,328	4.87	L. Occipital fusifrom gyrus
	R. Occipital pole	20	−102	−6		4.85	R. Occipital fusifrom gyrus
	R. Occipital pole	12	−96	2		4.81	
	R. Occipital pole	8	−92	0		4.79	
	R. Lingual gyrus	14	−88	−8		4.73	
	L. Lingual gyrus	−8	−88	−8		4.72	
XR-NTX effects on odor response-activation (Fig. 6)							
1	L. Precentral gyrus	−54	−10	50	8256	3.55	R. Frontal orbital cortex
	L. Postcentral gyrus	−28	−32	56		3.45	L. Frontal pole
	L. Postcentral gyrus	−48	−18	46		3.45	R. Cingulate gyrus
	L. Postcentral gyrus	−28	−28	72		3.42	R. Angular gyrus
	L. Precentral gyrus	−42	−14	52		3.38	R. Supramarginal gyrus, posterior division
	L. Postcentral gyrus	−60	−18	42		3.23	R. Supramarginal gyrus, anterior division
2	L. Paracingulate gyrus	−6	56	8	3224	3.26	L. Superior parietal lobule
	R. Frontal pole	30	44	−10		3.25	
	R. Frontal pole	24	46	6		3.20	
	R. Frontal pole	30	60	6		3.17	
	R. Frontal pole	24	44	12		3.16	
	R. Paracingulate gyrus	10	44	16		3.05	

(continued on next page)

Table 2 (*continued*)

Cluster	Activation extrema (region)	MNI x	MNI y	MNI z	Extent (mm^3)	Z	Other regions
XR-NTX effects on odor response-activation (Fig. 6)							
3	R. Anterior supramarginal gyrus	66	−28	34	3008	3.89	
	R. Anterior supramarginal gyrus	62	−28	32		3.86	
	R. Anterior supramarginal gyrus	56	−24	28		3.39	
	R. Anterior supramarginal gyrus	62	−34	44		3.38	
	R. Posterior superior temporal gyrus	66	−30	18		3.34	
	R. Parietal operculum cortex	66	−30	22		3.20	
4	R. Precentral gyrus	26	−24	60	2936	3.64	
	R. Postcentral gyrus	34	−30	68		3.30	
	R. Precentral gyrus	28	−22	68		3.24	
	R. Precentral gyrus	30	−16	66		3.18	
	R. Postcentral gyrus	40	−24	54		3.15	
	R. Precentral gyrus	32	−24	64		3.12	
XR-NTX effects on picture response-activation (Fig. 7)							
1	L. Frontal pole	−50	42	12	5576	4.21	L. Frontal orbital cortex
	L. Frontal pole	−28	46	34		4.00	R. Paracingulate gyrus
	L. Frontal pole	−44	46	20		3.87	R. Cingulate gyrus
	L. Inferior frontal gyrus, pars opercularis	−58	18	28		3.78	L. Middle frontal gyrus
	L. Frontal pole	−34	52	22		3.63	
	L. Frontal pole	−30	56	22		3.51	
2	R. White matter	12	34	−8	5024	3.88	
	R. White matter	16	44	−8		3.88	
	L. White matter	−16	38	−14		3.63	
	L. Subcallosal cortex	−8	26	−14		3.62	
	L. Frontal medial cortex	−2	46	−16		3.32	
	R. Frontal medial cortex	8	42	−14		3.27	

activation were prominent after presentation of odor cues. Deactivation was widespread among a number of prefrontal, cingulate, and lateral occipital cortex while activation was greatest in limbic regions and some white matter (Fig. 5, top and middle rows). As expected, increased brain activation was observed primarily in visual cortex in response to alcohol-related pictures (Fig. 5, bottom row).

Two scans were performed: one at baseline and another two weeks after a single i.m. injection of either XR-NTX (N = 15) or matched placebo (N = 13). Analysis of the BOLD signal changes during exposure to both alcohol-related odors and pictures revealed a number of significant differences between the placebo and active XR-NTX groups, when comparing the first and second scanning visits. The most salient differences were reductions in brain activation in the XR-NTX-treated group compared to the placebo-treated group for both visual and olfactory cues. Decreases in the response to alcohol odors (Fig. 6) were significant at $p < 0.000008$ and involved primarily superior frontal gyrus (self-awareness, coordination and sensory processing), supramarginal gyrus (Brodman 40—reading), postcentral gyrus (sensory), angular gyrus (Brodman 39—language, mathematics and cognition). No brain regions showed significant increases in response to alcohol odor cues.

Decreases in responses to the alcohol-related picture cues (Fig. 7) were significant at $p < 0.0006$. Differences were most pronounced in orbital gyri (integration of emotion, cognition, reward and punishment), cingulate gyrus (emotion, learning/memory), inferior frontal gyrus (speech), and middle frontal gyrus (face recognition, word meaning). No brain regions showed significant increases in response to alcohol picture cues.

Discussion

While other laboratories have used brain imaging to demonstrate that alcohol-related cues activate brain regions associated with reward and that medications can attenuate that response, this is the first study to demonstrate that injectable naltrexone decreases reactivity to both alcohol-related olfactory and visual cues in alcohol-dependent persons undergoing treatment. Furthermore, the olfactory cues were chosen on the basis of each individual's preference, making the cue exposure session even more salient to each participant. In both paradigms, the cue response attenuation was detected in the absence of alcohol administration itself, suggesting a mechanism by which XR-NTX may exert its clinical effect of prolonging initial abstinence and maintaining continued abstinence over time.

The present study found that there are systematic brain activation/deactivation patterns in response to both olfactory and visual alcohol cues. Visual cues have been used previously in this population (Myrick et al., 2008), but while imaging modalities such as EEG and event-related potentials have been used to track olfactory cues (Lorig, 1994), this is the first study using fMRI to identify the areas that are affected by olfactory stimuli in an alcohol-dependent population.

To understand craving, scientists must identify the brain mechanisms that lead to urges. To account for all manifestations of craving, both conscious and unconscious processes must be taken into account (Anton, 2000). Many researchers and clinicians consider craving an important contributor to the development and maintenance of alcohol dependence (Tiffany and Conklin, 2000). Craving has been described as a powerful urge to drink or as intense thoughts about alcohol, and The *International Classification of Diseases* (*ICD–10*) includes craving as an optional diagnostic criterion for addiction to alcohol or other drugs. Both the World Health Organization and the American Psychiatric Association define the term as a strong desire or sense of compulsion to take the drug (APA, 1994; WHO, 1992).

Acute alcohol administration results in a variety of effects and when sensitive instruments are used, a clear sense of euphoria occurs (Lukas and Mendelson, 1988; Lukas et al., 1986a,b, 1989, 1990). When a behavior is reinforced or the individual has a positive experience, it leads to an increased incidence of that behavior (in the case of

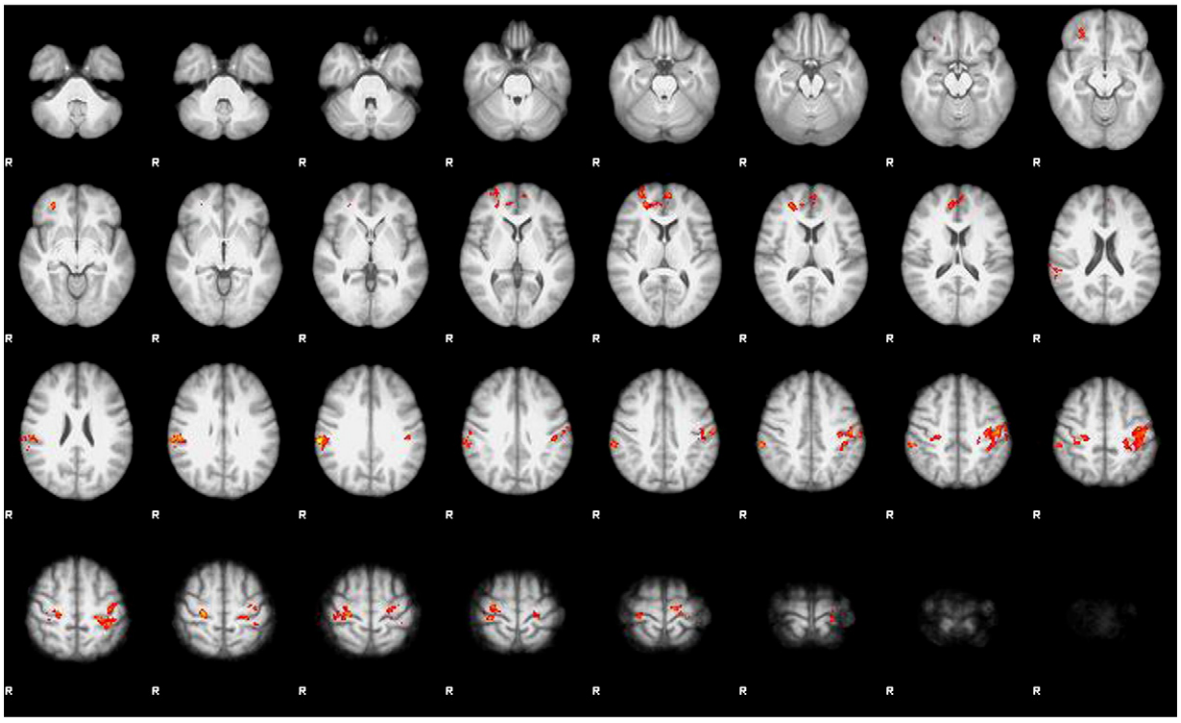

Fig. 6. Axial slices depicting changes in BOLD activation. Color-coding identifies regions where the response to alcohol odors was more attenuated in the XR-NTX-treated group compared to the placebo-treated group, second scan vs. first scan (red corresponds to z = 2.3, yellow to z = 4.2).

alcohol—drinking) and the cycle continues (Singleton and Gorelick, 1998). The rewarding effects of alcohol are thought to be mediated via release of endogenous opioids that then facilitates mesolimbic dopamine activity (Gianoulakis et al., 1996). As an opiate receptor antagonist, naltrexone would block this response and has actually been shown to reduce alcohol-induced increased dopamine activity in nucleus accumbens (Benjamin et al., 1993). Naltrexone also appears to dampen alcohol-induced stimulation (Drobes et al., 2004) and decreases subjective reports of "liking" (McCaul et al., 2000).

The process of craving is accelerated by the presence of objects, environments, or emotions that have been previously associated with alcohol consumption as they can produce a response that is as powerful as alcohol itself. Such stimuli/cues may include the sight of a bar, liquor

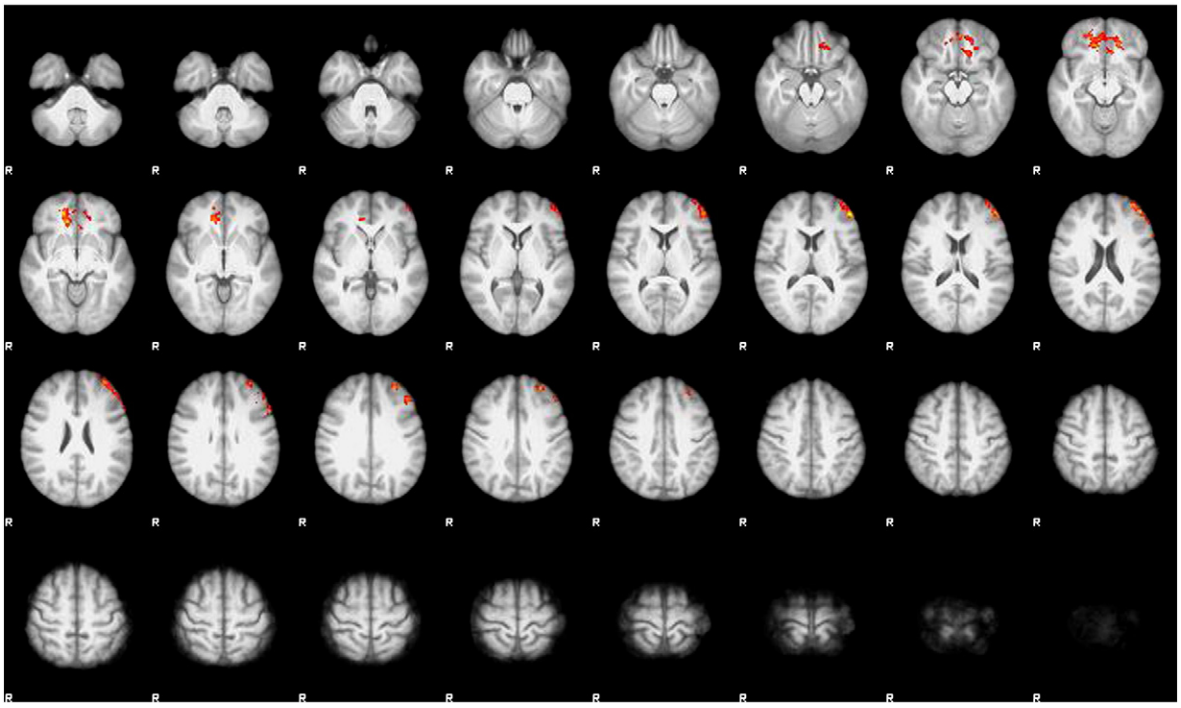

Fig. 7. Axial slices depicting changes in BOLD activation. Color-coding identifies regions where the response to alcohol-related pictures was more attenuated in the XR-NTX-treated group compared to the placebo-treated group, second scan vs. first scan (red corresponds to z = 2.3, yellow to z = 4.4).

store, or beverage advertisement; the company of friends who drink; or exposure to alcohol itself (Heinz et al., 2002). An abstinent alcoholic exposed to appropriate cues will experience a conscious urge, or craving, for alcohol (Drummond, 2001). It has been suggested that cue-elicited craving during or after treatment can trigger conscious coping strategies aimed at maintaining abstinence, and the success of coping depends on a drinker's confidence in their ability to resist the urge to drink (Anton, 1999). It is important to note that craving is only one of the several factors necessary to induce relapse (Rohsenow and Monti, 1999), but can be a powerful element. Naltrexone reduces the urge to drink (Monti et al., 2001; Ray and Hutchison, 2007) and the present study provides some evidence that this is mediated by reducing BOLD activation in brain regions that mediate self-awareness, cognition, emotion and reward.

Alcohol consumption may initiate the process of reinforcement by activating brain reward structures located in the limbic system and primarily consisting of the hypothalamus, amygdala, hippocampus, septal nuclei, anterior cingulate nucleus, nucleus accumbens, and ventral tegmental area (Carlezon and Thomas, 2009; Childress et al., 1999; Koob and Nestler, 1997). The reward center is linked to other brain areas involved in aspects of emotion, learning, and memory (Kelley, 2004). Interactions among these sites could account for the processes by which 1) emotion-laden memories of past positive drinking experiences become associated with cues, and 2) exposure to such cues can activate the reward center in the absence of alcohol, potentially leading to craving during abstinence. These processes are unconscious. However, the reward center also communicates with brain areas that appear to underlie higher intellectual (i.e., cognitive) functions such as judgment and decision-making. Because of this, heavy drinking may ultimately impair conscious processes that support the ability to cope with drinking urges (Anton, 1999). The fact that the reductions in BOLD signal strength to olfactory cues occurred in numerous cortical regions offers support for this notion and that the concept of craving cannot be thought of simply affecting basic reward processes.

In the present study, we found that alcohol-related visual and olfactory cues elicited significant increases in orbital and cingulate gyri, inferior frontal and middle frontal gyri and that these patterns of brain activation were significantly attenuated in XR-NTX-treated individuals. In order to measure this, alcohol-related visual and olfactory cues were presented to recently detoxified individuals while they received an fMRI scan. The alcohol cues produced the expected increased activation in specific brain regions. The subjects were randomized to receive either XR-NTX or placebo, given as a single i.m. injection. Two weeks later, the fMRI assessment was repeated along with the cue exposure paradigm. Those who had been treated with XR-NTX experienced a marked alterations in cue-induced brain activation in regions of the brain that are typically associated with sensory, cognitive, emotional, learning/memory and reward. Self-reports of craving for alcohol were also reduced during the 28-min session, but there was no overall significant effect on craving and therefore the effects on craving during the scanning procedure were modest. Thus, XR-NTX may alter the salience of both olfactory and visual cues. To the extent that cue reactivity and cue-induced craving play a role in relapse to alcohol use, reductions in the brain's reaction to these cues may interrupt the processes that precede a "slip" and relapse, thus contributing to the ability of XR-NTX to maintain abstinence. The finding that brain activation patterns were affected in the absence of an effect on desire to "want" alcohol at first seems counter-intuitive. However, it is important to recognize that one of the major weaknesses of the measure that we used to record their desire for alcohol was that it was one-dimensional. It has been demonstrated that drug and alcohol craving is a multifaceted behavior (Potgieter et al., 1999; Singleton and Gorelick, 1998), and while the simplicity of the VAS used in the magnet certainly helped track a potentially transient subjective state, it came at the expense of obtaining a more multidimensional assessment of desire or craving for alcohol. Nevertheless, it is well known that drinking in an outpatient setting can be reduced while at the same time changes in craving are not detected.

It is important to note that these changes in BOLD signal activation were noted after only *two weeks* of XR-NTX treatment. All participants received the same amount of supportive therapy including weekly 1 h counseling sessions. Thus, the speed with which these brain changes occur suggest that naltrexone has a more immediate effect on brain function. This change in brain function is consistent with the relatively rapid appearance of clinical efficacy of even a few days after treatment has begun (Ciraulo et al., 2008). Thus, the positive temporal relationship between changes in cue reactivity and clinical efficacy suggests that changes in brain reactivity could very well be involved in naltrexone's ability to curb alcohol drinking.

The present study has a few limitations that need to be considered when interpreting the results. While the sample size is reasonable for an imaging study that utilizes stimuli presentation, it was not powered for a treatment study. Moreover, assessing the efficacy of XR-NTX in reducing alcohol consumption in an outpatient study cannot be performed after only one month of treatment, but again this was not an aim of the study. The study was also not powered to detect male vs. female differences in cue reactivity even though it is possible that women may respond differently to alcohol- (Seo et al., 2011) and smoking- (Saladin et al., 2012) related cues. It is generally believed that individualized cues are more salient to individuals and while we presented participants with the odor of their preferred alcoholic beverage, the picture set was standardized across all participants. We felt that providing individual visual stimuli would make the interpretation of the data too complicated.

Cue reactivity is a recognized predictor of relapse of drug and alcohol use (Cooney et al., 1997; Garland et al., 2012). The areas affected by the picture- and odor-related cues in the present study are significant because they engage a wide range of neuronal resources that process external stimuli and formulate appropriate emotional responses that not only contributes to the craving response, but also tap into reward processes. As enhanced craving and high reward after drinking contribute to relapse, the degree to which XR-NTX reduces the saliency of these cues may very well be responsible for its effect on interrupting the processes that precede a "slip" and furthermore should also reduce the likelihood that a slip (i.e., single drink), should it occur, would turn into relapsed drinking.

Acknowledgments

Disclosure statement

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Previous presentations

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