Depressive Symptomatology Is Associated With Smaller Reductions in Drug Cue Reactivity During Extended-Release Naltrexone Treatment of Opioid Use Disorder

Zhenhao Shi, PhD[a,*]; Xinyi Li, PhD[a]; Kyle M. Kampman, MD[a]; Anna Rose Childress, PhD[a]; Corinde E. Wiers, PhD[a]; and Daniel D. Langleben, MD[a]

The high incentive value attributed to a drug in substance use disorders leads to the heightened dopaminergic responses to drug-related conditioned stimuli (ie, cue reactivity),[1] stimulating drug-seeking behavior and promoting relapse.[2] The nucleus accumbens (NAcc) is the key brain region implicated in cue reactivity in general. Specifically, in opioid use disorder (OUD), greater NAcc response to opioid drug cues has been associated with heavier drug use.[3] The once-monthly injectable extended-release opioid antagonist naltrexone (XR-NTX) is an effective relapse prevention medication for OUD[4,5] that significantly reduces NAcc cue reactivity.[6,7] Depression and OUD are highly comorbid,[8,9] and both involve endogenous opioid dysregulation.[10,11] Patients with more severe depressive symptoms show poorer response to OUD treatment.[12–14] Here, we used functional magnetic resonance imaging (fMRI) to test the hypothesis that depressive symptomatology in OUD is associated with reduced sensitivity of subjective or neural indices of drug cue reactivity to the XR-NTX treatment of OUD.

Methods

We performed a secondary analysis on a previously described dataset.[6] Briefly, 23 detoxified OUD patients (9 female; 21–47 years old) were offered up to 3 monthly XR-NTX injections. Participants completed pre-treatment fMRI before the first injection and on-treatment fMRI approximately 2 weeks after the first injection. Each fMRI session included a cue reactivity task that presented drug-related, sexual, aversive, and neutral images. Before and after the task, participants reported craving for opioids on a 10-point scale (0 = none, 9 = extremely). Cue-induced craving was indexed by the change from before to after the task. The Beck Depression Inventory (BDI), which demonstrates good reliability and validity in the OUD population,[15,16] was administered approximately 1 week after the first injection.

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Preprocessed fMRI data were analyzed by modeling each stimulus category. The NAcc was defined as the a priori region of interest. Neural activity was evaluated by contrasting the drug, sexual, and aversive conditions with the neutral condition. Pearson correlation was performed between BDI scores and changes in cue-induced craving and NAcc drug cue reactivity (on-treatment minus pre-treatment). We also tested the correlation for sexual and aversive stimuli. Whole-brain analysis explored correlation in other brain regions.[17]

See the Supplementary Material and Shi et al[6] for additional details on the methods.

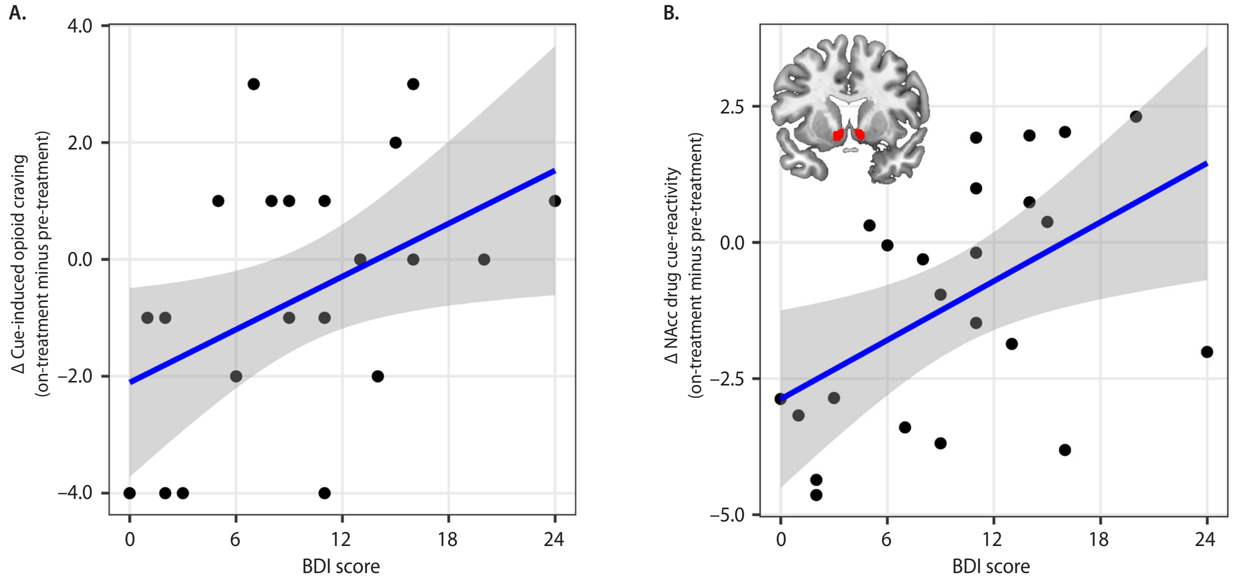
Results

Participants' BDI scores ranged from 0 (no depression) to 24 (moderate depression) (mean ± SD = 9.91 ± 6.22). A higher BDI score was associated with smaller reductions in cue-induced craving and NAcc cue reactivity at the ROI level (r = 0.44 and 0.50, P = .035 and .014; Figure 1) from pre-treatment to on-treatment. BDI score was not correlated with changes in NAcc response to sexual or aversive stimuli, (r = 0.21 and 0.07, P = .34 and .75). Whole-brain analysis did not show correlation with BDI score in other regions. See the Supplementary Material for additional results.

Discussion

Greater depressive symptoms were associated with smaller reductions in cue-induced craving and NAcc drug cue reactivity during XR-NTX treatment, suggesting that depression may hamper XR-NTX's ability to restore normal incentive salience processing. The lack of correlation between depressive symptoms and changes in NAcc response to the non-drug stimuli is consistent with our prior observation that XR-NTX effect was specific to drug cues.[6] Although there is no evidence of XR-NTX causing depression,[18–20] patients with greater depressive symptoms show more drug-related thoughts during XR-NTX treatment.[21] Our data corroborate this finding and point to NAcc as a key region mediating the impact of depressive symptoms on XR-NTX effectiveness. Given that depression and OUD are highly comorbid,[9] interventions targeting depressive symptoms may improve XR-NTX treatment success.[22] Study limitations include small sample size, potential confounds in the visual stimulus parameters, and limited number of follow-up timepoints (see Supplementary Material). Future studies are needed to confirm our findings and explore other factors that contribute to individual differences in relapse vulnerability.

Figure 1. (A) Correlation Between BDI Score and Change in Cue-Induced Opioid Craving and (B) Correlation Between BDI Score and Change in NAcc Drug Cue Reactivity[a]



[a]The anatomically defined NAcc region of interest (red) is shown at y = 10 in the Montreal Neurologic Institute space. The gray-shaded areas represent 95% confidence intervals.
Abbreviations: BDI = Beck Depression Inventory, NAcc = nucleus accumbens.

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See supplementary material for this brief report at PSYCHIATRIST.COM.

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Supplementary Material

Title: Depressive Symptomatology Is Associated With Smaller Reductions in Drug Cue Reactivity During Extended-Release Naltrexone Treatment of Opioid Use Disorder

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List of Supplementary Material

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SUPPLEMENTARY INFORMATION

Depressive symptomatology is associated with smaller reductions in drug cue reactivity during extended-release naltrexone treatment of opioid use disorder

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Inclusion and exclusion criteria

The DSM-IV-TR diagnosis of opioid dependence was established using the best estimate format based on all available sources of information, including history, the Mini International Neuropsychiatric Interview (MINI) for DSM-IV [1] and the Addiction Severity Index 5th Edition [2]. Four participants met the criteria for a current major depressive episode. However, it should be noted that diagnosis of major depressive episode in individuals in early recovery from OUD is challenging because of the differential diagnosis of substance-induced mood disorder and adjustment disorder with depressed mood.

Inclusion criteria were age between 18 and 59 years; a DSM-IV-TR diagnosis of opioid dependence confirmed by self-report and medical records documenting daily opioid use for more than 2 weeks in the past 3 months; evidence of detoxification from opioids before XR-NTX injections, established by urine drug screen (UDS) (Redwood Toxicology Laboratory, Santa Rosa, CA) and a negative naloxone challenge test; and good physical health ascertained by history and physical examination, blood chemistry and urinalysis.

Exclusion criteria were current use of medications that could confound blood oxygen level-dependent fMRI response, such as antidopaminergic agents, anticonvulsants, and β-blockers; current psychosis, dementia, intellectual disability, or lifetime history of schizophrenia; clinically significant cardiovascular, hematologic, pulmonary, hepatic, renal, metabolic, gastrointestinal, neurologic, or endocrine abnormalities; pregnancy or breastfeeding; history of clinically significant head trauma; contraindications for XR-NTX, such as medical conditions requiring opioid analgesics such as chronic pain disorder, planned surgery, obesity, elevated liver enzymes > 3 times the upper limit of normal, or failure to complete opioid detoxification; contraindications for MRI, such as indwelling magnetically active foreign bodies, or fear of enclosed spaces; and current use of illicit drugs (e.g., cocaine) except cannabis.

Study medication

To ensure completeness of opioid detoxification, XR-NTX was preceded by a challenge with 0.6 mg of naloxone hydrochloride IV. Participants were offered up to three monthly intramuscular injections of XR-NTX (380 mg of naltrexone-HCl gradually released from dissolvable polymer microspheres over a period of one month, manufactured by Alkermes Inc, Cambridge, MA, under the brand name Vivitrol®). As part of consent procedure, participants were briefed about the expected loss of pharmacological effects of opioids resulting from the XR-NTX treatment, and the dangers of attempting to overcome the opiate receptor blockade with higher than usual opioid doses [3,4]. Medication was provided in the context of ongoing psychosocial support (two weekly sessions of professional drug counseling and anti-relapse strategies by trained clinical psychologists) and twice-weekly UDS monitoring. Plasma concentrations of naltrexone and 6-β-naltrexol (an active metabolite of naltrexone) were measured on the day of the on-treatment session, using established liquid chromatography and tandem mass spectrometry technique [5,6]. Upon study completion, continuation of care was discussed with the participants, and they were given referrals to treatment providers in the community.

fMRI cue-reactivity paradigm

Drug cues were of two sub-categories: heroin and prescription opioids. Participants who used heroin exclusively or as their drug of choice were shown heroin-related images as drug cues; participants who used prescription opioids exclusively or as their drug of choice were shown images of common prescription opioid pills (Vicodin, Percocet, Oxycontin, etc.) and preparation for their use. All drug-related images were selected from our laboratory archive and were validated in previous studies [6-8]. The neutral stimuli were from our collection of non-drug images (building facades, people engaged in everyday activities, etc.) that have been previously used in studies of cue-reactivity in substance use disorders [6-9]. For male and female participants, sexual stimuli were selected from the erotic pictures in the International Affective Picture System (IAPS) and from our own stimulus archive that fell into the top quartile of pleasantness based on the male and female IAPS normative ratings, respectively. Aversive stimuli were selected from IAPS pictures that fell into the bottom quartile of pleasantness based on the overall normative ratings.

During each fMRI session, participants viewed the four categories of cues (drug, sexual, aversive and neutral). Each stimulus category included 24 unique images that were presented twice, resulting in a total of 192 trials. Each trial of the fMRI cue-reactivity task consisted of a stimulus displayed for 500 ms followed by a crosshair displayed for 1500 ms. The stimulus trials were interspersed with 48 baseline periods during which crosshairs were displayed for 2000 ms. Pseudorandom order of the stimuli trials and baseline periods was generated using optseq2 (https://surfer.nmr.mgh.harvard.edu/optseq). The task duration was 8 minutes, 28 seconds.

fMRI data acquisition and analysis

MRI data were collected using a Siemens Tim Trio 3 T system with a 32-channel head coil and a mirror that allowed participants to see the screen. Blood oxygen level-dependent (BOLD) fMRI was performed, using a whole-brain, single-shot gradient-echo echo-planar sequence with repetition time (TR)/echo time (TE) = 2000/30 ms, field of view (FOV) = 220×220 mm², matrix = 64×64, slice thickness/gap = 4.5/0 mm, 32 slices, effective voxel resolution of $3.4 \times 3.4 \times 4.5$ mm³, flip angle (FA) = 90°. After BOLD fMRI, MPRAGE T1-weighted images were acquired with TR/TE = 1510/3.71 ms, FOV = 256×192 mm², matrix = 256×192, slice thickness/gap = 1/0 mm, 160 slices, effective voxel resolution of $1 \times 1 \times 1$ mm³, FA = 9°. An oblique acquisition, oriented along the anterior commissure–posterior commissure line allowed coverage of the entire brain with the exception of the lower cerebellum.

Using SPM 12 (Wellcome Trust Centre for Neuroimaging), functional MRI images were adjusted for slice timing, realigned to the first scan to correct for head motion, spatially smoothed by a Gaussian filter with full width at half maximum (FWHM) set to 8 mm, and normalized into stereotactic Montreal Neurological Institute (MNI) space with 2-mm cubic voxels. Individual-level statistical analyses were performed voxel-wise by modeling drug, sexual, aversive, and neutral stimuli using a canonical hemodynamic response function as well as its derivatives with respect to time and dispersion. Effects of drug, sexual and aversive stimuli were contrasted with the neutral stimuli. The NAcc was anatomically defined using the Harvard-Oxford Atlas (https://www.fmrib.ox.ac.uk/fsl). Contrast values for drug, sexual and aversive stimuli during the pre-treatment and on-treatment sessions were extracted from the NAcc ROI. Changes in the contrast values (on-treatment minus pre-treatment) were subjected to analysis of Pearson correlation with BDI score. We performed exploratory whole-brain regression analysis to examine whether BDI score was associated with drug cue-reactivity in regions other than the NAcc. In the whole-brain analysis, BDI score was entered as an independent variable in a linear regression model against the change in neural response to drug stimuli (on-treatment minus pre-treatment). Significant regions were determined using the threshold-free cluster-enhancement (TFCE) algorithm at cluster-level Bonferroni-corrected $p < 0.05$ [10].

Head movement during fMRI data acquisition

None of the participants met the criterion for exclusion due to excessive head movement that was set at > 1 voxel. The absolute movement and framewise displacement were both low at the pre-treatment session (root mean square = 0.19 ± 0.08 & 0.19 ± 0.14 mm) and the on-treatment session (0.19 ± 0.06 & 0.20 ± 0.12 mm). To investigate the potential impact of task stimuli on head movement, we fitted linear mixed effects models for absolute movement and framewise displacement that included fixed effects for the four types of cues (drug, sexual, aversive, neutral) as well as random intercepts and slopes for each individual and timepoint. We found that the cues were not significantly associated with either absolute movement or framewise displacement ($F(4,11679) = 0.69$ & 0.54, $p = 0.60$ & 0.71).

Cue-reactivity at the pre-treatment session

As a manipulation check, we examined cue-induced craving and NAcc cue-reactivity at the pre-treatment session. Specifically, we performed a paired t-test (pre-fMRI vs. post-fMRI) on pre-treatment craving and repeated-measures one-way ANOVA of the effect of Stimulus (drug vs. sexual vs. aversive) on pre-treatment NAcc response. There was a significantly increase in craving from pre-fMRI to post-fMRI ($t(22) = 2.55$, $p = 0.018$; see Fig S1, left panel). We also found a significant Stimulus effect ($F(2,44) = 7.44$, $p = 0.002$; see Fig S1, right panel) that was driven by a significantly greater NAcc response to drug stimuli than to sexual or aversive stimuli (Bonferroni-corrected $p = 0.015$ & 0.015) and no significant difference between the sexual and aversive stimuli (Bonferroni-corrected $p = 0.39$). These results confirm the validity of the cue-reactivity paradigm.

Change in cue-reactivity from pre-treatment to on-treatment

Repeated-measures 2×2 ANOVA tested the effects of Session (pre-treatment vs. on-treatment) and Time (pre-fMRI vs. post-fMRI) on craving. We found significant main effects of Session ($F(1,22) = 34.27$, $p < 0.001$) and Time ($F(1,22) = 5.86$, $p = 0.24$), such that craving decreased from pre-treatment to on-treatment and increased from pre-fMRI to post-fMRI (see Fig S1, left panel). The Session×Time interaction was not significant ($F(1,22) = 1.88$, $p = 0.18$).

We also performed repeated-measures 2×3 ANOVA on NAcc response to test the effects of Session (pre-treatment vs. on-treatment) and Stimulus (drug vs. sexual vs. aversive). We found a significant Session×Stimulus interaction ($F(2,44) = 5.86$, $p = 0.006$; see Fig S1, right panel). Post-hoc comparisons showed a significant reduction of NAcc drug cue-reactivity from pre-treatment to on-treatment (Bonferroni-corrected $p = 0.029$), but no significant change in response to sexual or aversive stimuli (Bonferroni-corrected $p = 0.21$ & 0.20).

The results above are consistent with previous findings that XR-NTX reduces overall opioid craving [11,12] and brain response to drug cues [6,7]. However, while Wang et al[13] found a reduction in cue-induced opioid craving during XR-NTX treatment, such a reduction was not statistically significant in the current analysis. The inconsistency may be due to small sample size and limited reliability of the craving scale [14,15]. Future research with a larger sample and improved craving measurement is warranted.

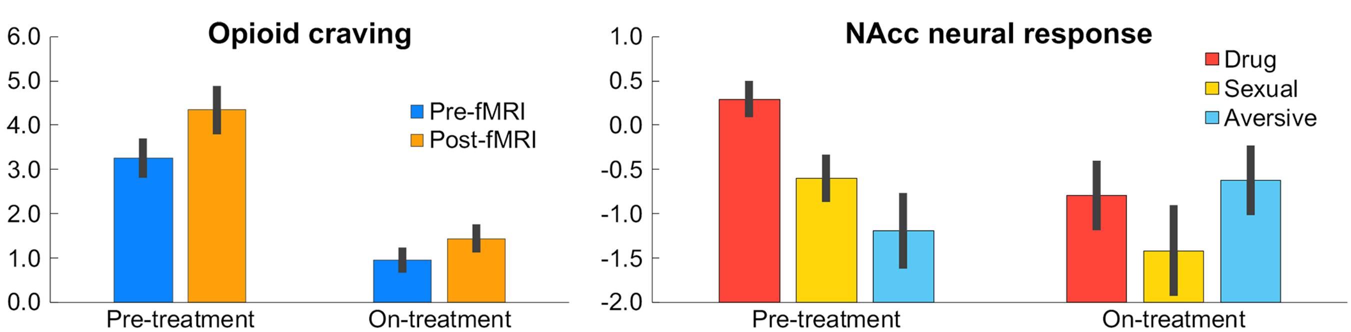

Fig S1. Raw data of opioid craving (left) and NAcc neural response (right). Abbreviations: fMRI, functional magnetic resonance imaging; NAcc, nucleus accumbens.

Correlation results for raw cue-reactivity indices

We explored whether BDI score was associated with any of the raw opioid craving sores. We found that for the pre-treatment session, BDI score was not correlated with opioid craving either before the cue-reactivity task ($r = 0.07$, $p = 0.74$) or after the cue-reactivity task ($r = –0.20$, $p = 0.36$). For the on-treatment session, BDI score was not correlated with opioid craving before the cue-reactivity task ($r = 0.29$, $p = 0.18$), but was positively correlated with craving after the cue-reactivity task ($r = 0.43$, $p = 0.041$).

We also explored whether BDI score was associated with pre-treatment and on-treatment NAcc drug cue-reactivity, respectively. We found that BDI score was not correlated with pre-treatment NAcc drug cue-reactivity ($r = –0.32$, $p = 0.13$), but was positively correlated with on-treatment NAcc drug cue-reactivity ($r = 0.43$, $p = 0.040$).

Analyses of secondary assessments

In addition to the initial BDI scores collected before the on-treatment MRI session, we also administered BDI during biweekly follow-up visits up until approximately 12 weeks after the on-treatment MRI session (see Table S1). There was, however, an increase in attrition rates (from week 2 to 12: 13%, 26%, 39%, 52%, 52%, 57%). We used a mixed effects model with individual-specific random intercepts and slopes to examine the change in BDI score across time. We found that BDI score decreased significantly from the initial timepoint to 12 weeks after the on-treatment MRI scan ($t(104) = –6.02$, $p < 0.001$). Changes in cue-induced craving and NAcc drug cue-reactivity from pre-treatment to on-treatment was not associated BDI scores obtained at any of the follow-up timepoints ($|rs| < 0.29$, $ps > 0.26$).

Table S1. Beck Depression Inventory scores at all timepoints

	Initial	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**
mean±SD	9.91±6.22	7.10±8.50	4.82±6.15	5.36±7.30	1.82±3.03	2.64±4.61	2.20±3.46
N	23	20	17	14	11	11	10

We performed additional analyses on the following baseline characteristics: 1) demographics, including age, sex, and years of education; 2) drug use severity assessed by the Addiction Severity Index drug composite score [2,16]; 3) years of opioid use; 4) number of days since last opioid use; 5) smoking severity assessed by the number of cigarettes smoked per day; 6) pre-treatment and on-treatment use of opioid, cannabis, and stimulant assessed by UDS; and 7) cannabis, alcohol and stimulant use disorders, indexed by abuse or dependence diagnosed by the MINI [1]. We examined the extent to which these baseline characteristics were associated with the variables of interest, i.e., BDI score and changes in cue-induced craving and NAcc drug cue-reactivity from pre-treatment to on-treatment. Pearson correlation and two-sample t-test were used for continuous and dichotomous variables, respectively (with the exception of concurrent tobacco, opioid, and stimulant use due to small subsample sizes). Descriptive statistics of the baseline characteristics are reported in Table S2. Except for a positive correlation between the number of days since last opioid use and the change in cue-induced craving ($r = –0.49$, $p = 0.017$), we did not find any other significant associations between baseline characteristics and the variables of interest ($ps > 0.083$). We also compared the participants who had comorbid cannabis, alcohol, or stimulant use disorders (N = 14) to those who did not have any of those comorbidities (N = 7) and found a significant difference in the change in cue-induced craving ($t(21) = –2.59$, $p = 0.017$). After controlling for the number of days since last opioid use and the presence of comorbid cannabis, alcohol, or stimulant use disorders, the correlation between BDI score and the change in cue-induced craving remained significant ($r = 0.44$, $p = 0.047$).

Table S2. Baseline characteristics

Variable	**mean±SD or N**
Age	30.65±8.38
Sex	14 male, 9 female
Years of education	13.83±2.46
Addiction Severity Index drug composite score	0.26±0.10
Years of opioid use	8.87±8.15
Number of days since last opioid use	21.39±20.03
Tobacco cigarette smoking	22
Number of cigarettes per day (among daily smokers)	10.22±8.72
Concurrent opioid use (pre-/on-treatment)	0/0
Concurrent cannabis use (pre-/on-treatment)	3/3
Concurrent stimulant use (pre-/on-treatment)	0/1
Cannabis use disorder	6
Alcohol use disorder	4
Stimulant use disorder	9

Potential impact of stimulus characteristics

All stimulus categories (heroin, prescription opioid, male sexual, female sexual, aversive, and neutral) had the same number of unique stimuli, and all stimuli were color images of the same size presented at the center of a uniformly black background. We calculated image luminance and contrast using the CIELAB color model and the root-mean-square contrast algorithm, respectively. One-way ANOVAs showed a significant effect of stimulus category on luminance and contrast ($F(5,138) = 38.61$ & 21.95, $ps < 0.001$). Pairwise comparisons with Bonferroni correction showed that the heroin stimuli had lower luminance and contrast than all the other stimulus categories ($ps < 0.001$). Stimulus categories other than heroin did not differ between each other ($ps > 0.12$). To determine if either luminance or contrast was a confounding variable, we examined the effect of heroin vs. prescription opioid stimuli, which differed in luminance and contrast. First, a repeated-measures ANCOVA tested the effects of Session (pre-treatment vs. on-treatment) and Stimulus (drug vs. sexual vs. aversive) on NAcc response while controlling for drug stimulus type (heroin vs. prescription opioid). We found that the Time×Stimulus interaction remained significant ($F(2,42) = 3.36$, $p = 0.044$) and was driven by a significant reduction in NAcc response to drug ($p = 0.33$) but not sexual or aversive stimuli ($p = 0.21$ & 0.22). Drug stimulus type did not show significant main effect or any interaction ($ps > 0.45$). Second, partial correlations showed that the association between BDI score and change in cue-reactivity (including cue-induced craving and NAcc response to drug cues) remained significant while controlling for drug stimulus type ($r = 0.44$ & 0.51, $p = 0.041$ & 0.016). Taken together, the lack of impact of drug stimulus type on our study findings suggests that image luminance and contrast were unlikely to be confounding variables.

An unrelated group of OUD patients rated the emotion reaction to each image on a 9-point scale (1 = the least pleasant; 9 = the most pleasant). One-way ANOVA showed a significant effect of stimulus category on emotion reaction ($F(5,138) = 139.69$, $p < 0.001$). Pairwise comparisons showed no difference between heroin, prescription opioid, and neutral stimuli ($ps = 1.00$), and no difference between male and female sexual stimuli ($p = 1.00$). Both male and female sexual stimuli were rated as more pleasant than all other stimuli ($ps < 0.001$), while aversive stimuli were rated as least pleasant ($ps < 0.001$). The qualitatively different results of the emotion reaction (sexual > drug > aversive) and NAcc response (drug > sexual ≈ aversive) suggest that emotion reaction was unlikely to have confounded our study finding. Despite these reassuring findings, future studies are needed to systematically evaluate how the luminance and contrast of the visual drug cues and the associated non-specific emotional reactions may affect the neural indices of drug cue-reactivity. Future research is also needed to examine how sexual orientation modulates the brain response to drug cues relative to sexual cues in OUD [17,18].

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