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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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1 **SUPPLEMENTARY INFORMATION**

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

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22 **Inclusion and exclusion criteria**

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

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

34 Exclusion criteria were current use of medications that could confound blood oxygen level-dependent fMRI

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

8 **Study medication**

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

21 **fMRI cue-reactivity paradigm**

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

32 During each fMRI session, participants viewed the four categories of cues (drug, sexual, aversive and neutral). Each
33 stimulus category included 24 unique images that were presented twice, resulting in a total of 192 trials. Each trial of
34 the fMRI cue-reactivity task consisted of a stimulus displayed for 500 ms followed by a crosshair displayed for 1500

1 ms. The stimulus trials were interspersed with 48 baseline periods during which crosshairs were displayed for 2000
2 ms. Pseudorandom order of the stimuli trials and baseline periods was generated using optseq2
3 (<https://surfer.nmr.mgh.harvard.edu/optseq>). The task duration was 8 minutes, 28 seconds.

4 **fMRI data acquisition and analysis**

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

13 Using SPM 12 (Wellcome Trust Centre for Neuroimaging), functional MRI images were adjusted for slice timing,
14 realigned to the first scan to correct for head motion, spatially smoothed by a Gaussian filter with full width at half
15 maximum (FWHM) set to 8 mm, and normalized into stereotactic Montreal Neurological Institute (MNI) space with
16 2-mm cubic voxels. Individual-level statistical analyses were performed voxel-wise by modeling drug, sexual,
17 aversive, and neutral stimuli using a canonical hemodynamic response function as well as its derivatives with respect
18 to time and dispersion. Effects of drug, sexual and aversive stimuli were contrasted with the neutral stimuli. The
19 NAcc was anatomically defined using the Harvard-Oxford Atlas (<https://www.fmrib.ox.ac.uk/fsl>). Contrast values for
20 drug, sexual and aversive stimuli during the pre-treatment and on-treatment sessions were extracted from the NAcc
21 ROI. Changes in the contrast values (on-treatment minus pre-treatment) were subjected to analysis of Pearson
22 correlation with BDI score. We performed exploratory whole-brain regression analysis to examine whether BDI
23 score was associated with drug cue-reactivity in regions other than the NAcc. In the whole-brain analysis, BDI score
24 was entered as an independent variable in a linear regression model against the change in neural response to drug
25 stimuli (on-treatment minus pre-treatment). Significant regions were determined using the threshold-free cluster-
26 enhancement (TFCE) algorithm at cluster-level Bonferroni-corrected $p < 0.05$ ¹⁰.

27 **Head movement during fMRI data acquisition**

28 None of the participants met the criterion for exclusion due to excessive head movement that was set at > 1 voxel.
29 The absolute movement and framewise displacement were both low at the pre-treatment session (root mean square =
30 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
31 impact of task stimuli on head movement, we fitted linear mixed effects models for absolute movement and
32 framewise displacement that included fixed effects for the four types of cues (drug, sexual, aversive, neutral) as well
33 as random intercepts and slopes for each individual and timepoint. We found that the cues were not significantly
34 associated with either absolute movement or framewise displacement ($F(4,11679) = 0.69$ & 0.54 , $p = 0.60$ & 0.71).

1 Cue-reactivity at the pre-treatment session

2 As a manipulation check, we examined cue-induced craving and NAcc cue-reactivity at the pre-treatment session.
3 Specifically, we performed a paired t-test (pre-fMRI vs. post-fMRI) on pre-treatment craving and repeated-measures
4 one-way ANOVA of the effect of Stimulus (drug vs. sexual vs. aversive) on pre-treatment NAcc response. There was
5 a significantly increase in craving from pre-fMRI to post-fMRI ($t(22) = 2.55, p = 0.018$; see Fig S1, left panel). We
6 also found a significant Stimulus effect ($F(2,44) = 7.44, p = 0.002$; see Fig S1, right panel) that was driven by a
7 significantly greater NAcc response to drug stimuli than to sexual or aversive stimuli (Bonferroni-corrected $p = 0.015$
8 & 0.015) and no significant difference between the sexual and aversive stimuli (Bonferroni-corrected $p = 0.39$).
9 These results confirm the validity of the cue-reactivity paradigm.

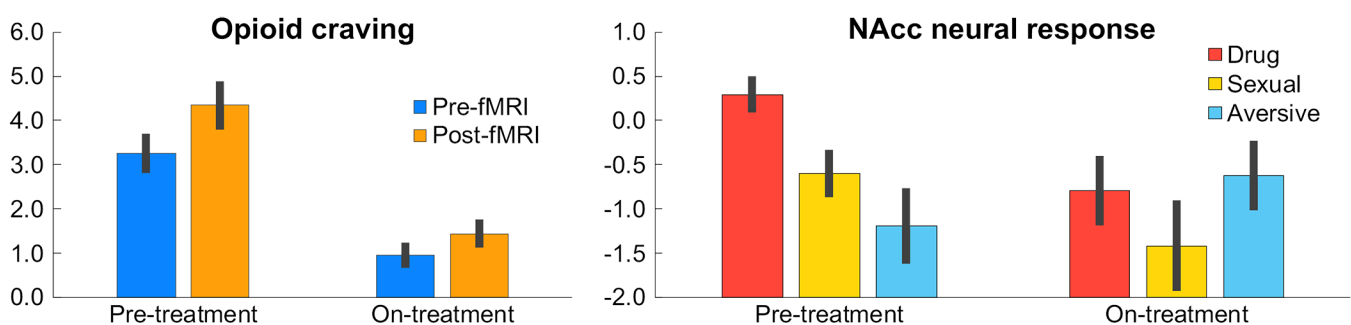
10 Change in cue-reactivity from pre-treatment to on-treatment

11 Repeated-measures 2×2 ANOVA tested the effects of Session (pre-treatment vs. on-treatment) and Time (pre-fMRI
12 vs. post-fMRI) on craving. We found significant main effects of Session ($F(1,22) = 34.27, p < 0.001$) and Time
13 ($F(1,22) = 5.86, p = 0.24$), such that craving decreased from pre-treatment to on-treatment and increased from pre-
14 fMRI to post-fMRI (see Fig S1, left panel). The Session \times Time interaction was not significant ($F(1,22) = 1.88, p =$
15 0.18).

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

21 The results above are consistent with previous findings that XR-NTX reduces overall opioid craving^{11,12} and brain
22 response to drug cues^{6,7}. However, while Wang et al¹³ found a reduction in cue-induced opioid craving during XR-
23 NTX treatment, such a reduction was not statistically significant in the current analysis. The inconsistency may be due
24 to small sample size and limited reliability of the craving scale^{14,15}. Future research with a larger sample and
25 improved craving measurement is warranted.

26



27

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

29

1

2 Correlation results for raw cue-reactivity indices

3 We explored whether BDI score was associated with any of the raw opioid craving scores. We found that for the pre-
4 treatment session, BDI score was not correlated with opioid craving either before the cue-reactivity task ($r = 0.07, p =$
5 0.74) or after the cue-reactivity task ($r = -0.20, p = 0.36$). For the on-treatment session, BDI score was not correlated
6 with opioid craving before the cue-reactivity task ($r = 0.29, p = 0.18$), but was positively correlated with craving after
7 the cue-reactivity task ($r = 0.43, p = 0.041$).

8 We also explored whether BDI score was associated with pre-treatment and on-treatment NAcc drug cue-reactivity,
9 respectively. We found that BDI score was not correlated with pre-treatment NAcc drug cue-reactivity ($r = -0.32, p =$
10 0.13), but was positively correlated with on-treatment NAcc drug cue-reactivity ($r = 0.43, p = 0.040$).

11 Analyses of secondary assessments

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

19

20

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

21

22 We performed additional analyses on the following baseline characteristics: 1) demographics, including age, sex, and
23 years of education; 2) drug use severity assessed by the Addiction Severity Index drug composite score^{2,16}; 3) years
24 of opioid use; 4) number of days since last opioid use; 5) smoking severity assessed by the number of cigarettes
25 smoked per day; 6) pre-treatment and on-treatment use of opioid, cannabis, and stimulant assessed by UDS; and 7)
26 cannabis, alcohol and stimulant use disorders, indexed by abuse or dependence diagnosed by the MINI¹. We
27 examined the extent to which these baseline characteristics were associated with the variables of interest, i.e., BDI
28 score and changes in cue-induced craving and NAcc drug cue-reactivity from pre-treatment to on-treatment. Pearson
29 correlation and two-sample t-test were used for continuous and dichotomous variables, respectively (with the
30 exception of concurrent tobacco, opioid, and stimulant use due to small subsample sizes). Descriptive statistics of the
31 baseline characteristics are reported in Table S2. Except for a positive correlation between the number of days since

1 last opioid use and the change in cue-induced craving ($r = -0.49$, $p = 0.017$), we did not find any other significant
 2 associations between baseline characteristics and the variables of interest ($ps > 0.083$). We also compared the
 3 participants who had comorbid cannabis, alcohol, or stimulant use disorders ($N = 14$) to those who did not have any
 4 of those comorbidities ($N = 7$) and found a significant difference in the change in cue-induced craving ($t(21) = -2.59$,
 5 $p = 0.017$). After controlling for the number of days since last opioid use and the presence of comorbid cannabis,
 6 alcohol, or stimulant use disorders, the correlation between BDI score and the change in cue-induced craving
 7 remained significant ($r = 0.44$, $p = 0.047$).

8
 9 **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

10

11 **Potential impact of stimulus characteristics**

12 All stimulus categories (heroin, prescription opioid, male sexual, female sexual, aversive, and neutral) had the same
 13 number of unique stimuli, and all stimuli were color images of the same size presented at the center of a uniformly
 14 black background. We calculated image luminance and contrast using the CIELAB color model and the root-mean-
 15 square contrast algorithm, respectively. One-way ANOVAs showed a significant effect of stimulus category on
 16 luminance and contrast ($F(5,138) = 38.61$ & 21.95 , $ps < 0.001$). Pairwise comparisons with Bonferroni correction
 17 showed that the heroin stimuli had lower luminance and contrast than all the other stimulus categories ($ps < 0.001$).
 18 Stimulus categories other than heroin did not differ between each other ($ps > 0.12$). To determine if either
 19 luminance or contrast was a confounding variable, we examined the effect of heroin vs. prescription opioid stimuli,
 20 which differed in luminance and contrast. First, a repeated-measures ANCOVA tested the effects of Session (pre-

1 treatment vs. on-treatment) and Stimulus (drug vs. sexual vs. aversive) on NAcc response while controlling for drug
2 stimulus type (heroin vs. prescription opioid). We found that the Time×Stimulus interaction remained significant
3 ($F(2,42) = 3.36, p = 0.044$) and was driven by a significant reduction in NAcc response to drug ($p = 0.33$) but not
4 sexual or aversive stimuli ($p = 0.21$ & 0.22). Drug stimulus type did not show significant main effect or any
5 interaction ($ps > 0.45$). Second, partial correlations showed that the association between BDI score and change in
6 cue-reactivity (including cue-induced craving and NAcc response to drug cues) remained significant while
7 controlling for drug stimulus type ($r = 0.44$ & $0.51, p = 0.041$ & 0.016). Taken together, the lack of impact of drug
8 stimulus type on our study findings suggests that image luminance and contrast were unlikely to be confounding
9 variables.

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

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