Pain Medicine, 22(9), 2021, 2019–2027
doi: 10.1093/pm/pnab031
Advance Access Publication Date: 24 February 2021
Original Research Article

Reward Responsiveness in Patients with Opioid Use Disorder on Opioid Agonist Treatment: Role of Comorbid Chronic Pain

Patrick H. Finan PhD,* Janelle Letzen, PhD* David H. Epstein, PhD,† Chung Jung Mun PhD,* Samuel Stull, BS,† William J. Kowalczyk, PhD,† Daniel Agage, MD,† Karran A. Phillips, MD,† Diego A. Pizzagalli, PhD,‡ and Kenzie L. Preston, PhD†

*School of Medicine, Johns Hopkins University, Baltimore, Maryland; †Intramural Research Program, National Institute on Drug Abuse, Baltimore, Maryland; ‡McLean Hospital and Harvard Medical School, Boston, Massachusetts, USA

Correspondence to: Patrick H. Finan, Johns Hopkins University School of Medicine, 5510 Nathan Shock Dr. Suite 100, Baltimore, MD 21224, USA. Tel: 410-550-7901; Fax: 410-550-0117; E-mail: pfinan1@jhu.edu.

Author William J. Kowalczyk is currently affiliated with Hartwick College, Oneonta, New York, USA.

Funding sources: This work was supported by the Intramural Research Program of the National Institute on Drug Abuse (NIDA), a career development grant awarded to PHF (NIH/NIDA K23DA035915), an R01 awarded to PHF (NIH/NIDA R01DA048206), and an postdoctoral fellowship award to CJM (NIH/NIDA F32DA049393). DAP was partially supported by R37 MH068376 from the National Institute of Mental Health.

Disclosure and conflicts of interest: Over the past 3 years, Dr. Pizzagalli has received consulting fees from Akili Interactive Labs, BlackThorn Therapeutics, Boehringer Ingelheim, Compass Pathway, Otsuka Pharmaceuticals, and Takeda Pharmaceuticals; one honorarium from Alkermes; and research funding from the National Institute of Mental Health, Dana Foundation, Brain and Behavior Research Foundation, and Millennium Pharmaceuticals. In addition, he has received stock options from BlackThorn Therapeutics. Dr. Pizzagalli has a financial interest in BlackThorn Therapeutics, which has licensed the copyright to the Probabilistic Reward Task through Harvard University. Dr. Pizzagalli's interests were reviewed and are managed by McLean Hospital and Partners HealthCare in accordance with their conflict-of-interest policies. No funding from these entities was used to support the present work, and all views expressed are solely those of the authors. All other authors declare no conflicts of interest. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Abstract

Objective. Evidence suggests that blunted reward responsiveness may account for poor clinical outcomes in both opioid use disorder (OUD) and chronic pain. Understanding how individuals with OUD and comorbid chronic pain (OUD+CP) respond to rewards is, therefore, of clinical interest because it may reveal a potential point of behavioral intervention. **Methods**. Patients with OUD (n = 28) and OUD+CP (n = 19) on opioid agonist treatment were compared on: 1) the Probabilistic Reward Task (an objective behavioral measure of reward response bias) and 2) ecological momentary assessment of affective responses to pleasurable events. **Results**. Both the OUD and the OUD+CP groups evidenced an increase in reward response bias in the Probabilistic Reward Task. The rate of change in response bias across blocks was statistically significant in the OUD group ($B = 0.06$, standard error [SE] = 0.02, $t = 3.92$, $P < 0.001$, 95% confidence interval [CI]: 0.03 to 0.09) but not in the OUD+CP group ($B = 0.03$, SE = 0.02, $t = 1.90$, $P = 0.07$, 95% CI: −0.002 to 0.07). However, groups did not significantly differ in the rate of change in response bias across blocks ($B = 0.03$, SE = 0.02, $t = 1.21$, $P = 0.23$, 95% CI: −0.02 to 0.07). Groups did not significantly differ on state measures of reward responsiveness (P's ≥0.50). **Conclusions**. Overall, findings across objective and subjective measures were mixed, necessitating follow-up with a larger sample. The results suggest that although there is a reward response bias in patients with OUD+CP treated with opioid agonist treatment relative to patients with OUD without CP, it is modest and does not appear to translate into patients' responses to rewarding events as they unfold in daily life.

Introduction

Reward responsiveness is a fundamental process that strongly and reliably drives behavior to approach rewarding stimuli and avoid stimuli associated with diminished reward value [1]. It can be assessed behaviorally, with tests of implicitly learned reward responsiveness [2], or subjectively, through both trait and state measures reflecting how individuals believe they appraise and react to rewarding stimuli [3–5]. Dopamine is an essential substrate of reward responsiveness [6], supporting cognitive and motivational states that fuel the pursuit of a wide array of natural rewards [7–11]. Opioids stimulate dopamine release, reinforcing the behavior to seek more opioid [12]. However, repeated exposure to exogenous opioids desensitizes endogenous opioid and dopamine receptor function in the context of naturally rewarding stimuli, in turn impairing reward responsiveness to natural rewards and promoting further drug seeking [13, 14]. Such theories are supported by pharmacogenomic evidence of dysfunctional dopamine signaling in patients with opioid use disorder (OUD) [15]. Clinically, reward responsiveness deficits are thought to underlie the elevated rates of anhedonia observed in early opioid addiction [16].

These broad links, however, risk oversimplifying a wide range of factors that could promote individual-level or group-level differences in reward responsiveness within the OUD population. Chronic pain is a particularly pernicious comorbidity of OUD; up to 60% of individuals with OUD on opioid agonist treatment (OAT) report chronic pain [17–19]. Moreover, chronic pain is associated with high rates of psychiatric comorbidities [20] and greater opioid craving [21] among patients with OUD on OAT. Intriguingly, there is a nascent but growing evidence base that suggests chronic pain may erode reward-related resources through neuroplastic changes within corticostriatal circuits [22–24]. Additionally, one small study reported lower levels of trait reward responsiveness in patients with chronic pain than in healthy controls [25]. Although those results have yet to be replicated, they raise the question of whether patients with OUD and comorbid chronic pain (OUD+CP) might show reduced levels of reward responsiveness relative to patients with OUD without chronic pain. Because chronic pain is highly prevalent in OUD, understanding its associations with core constructs of OUD pathology, such as reward responsiveness, can inform how treatments are conceptualized and tailored in this population.

In the present study, we examined reward responsiveness in OUD and OUD+CP patients by using a multimodal assessment approach, as concordant positive findings observed across multiple measurement modalities enhance the reliability of interpretations in small samples [26]. We assessed behavioral reward responsiveness with the Probabilistic Reward Task (PRT), a well-validated implicit learning task [2]. Additionally, we assessed reward responsiveness at the state level with ecological momentary assessment (EMA) questions related to the experience of pleasant activities in daily life. All participants were being treated with a standard OAT involving maintenance on a mu-opioid agonist (i.e., methadone or buprenorphine/naloxone). We hypothesized that, compared with patients with OUD without chronic pain, OUD+CP patients would show evidence of attenuated reward responsiveness in two ways: 1) a flattened reward responsiveness curve across blocks on the PRT and 2) lower ratings of daily pleasure.

Methods

Overview

To address the present study's aim of examining reward processing differences between OUD and OUD+CP patients undergoing OAT, we examined data from a larger parent project from the National Institute of Drug Abuse's Intramural Research Program (NIDA IRP) in Baltimore, Maryland, USA. Data for the present project were collected between April 2015 and October 2017. The NIDA Institutional Review Board approved all the study procedures, and all participants provided written informed consent before participation. Only methods germane to the present study's aims are described, and additional methods from the parent project can be found in previous work [27–29].

Participants

Fifty-six participants enrolled in the study. However, eight were excluded from analysis because of violations of data quality thresholds on the PRT (described later). One additional individual was an influential outlier on PRT data and was removed. The PRT data for this individual, who was in the OUD+CP group, had the effect of exaggerating the primary group comparison on PRT slopes. Removing this individual reduced the magnitude of group difference observed. After these exclusions, the final sample for this study was 47 individuals (OUD+CP: n = 19; OUD: n = 28). We recruited participants by using fliers at local outpatient treatment facilities and newspaper advertisements. Individuals seeking OUD treatment were eligible if they were 1) enrolled in the NIDA IRP's office-based outpatient treatment (OBOT) program or 2) already enrolled in OUD treatment elsewhere (TE) in the community. Inclusion criteria for OBOT participants included 1) age between 18 and 75 years and 2) physical dependence on opioids confirmed by positive urine and/or frank opioid withdrawal. OBOT cohort participants were excluded if they met criteria for any of the following: 1) a history of any *Diagnostic and Statistical Manual* (DSM)-5 diagnosis of psychotic disorder or bipolar disorder or ongoing Major Depressive Disorder, 2) current alcohol-use disorder or sedative-hypnotic-use disorder, 3) cognitive impairment that would preclude informed

consent or valid self-report, 4) any condition that would interfere with urine collection, or 5) current medical illness (e.g., cirrhosis, nephrotic syndrome, etc.) or use of medications (e.g., glucocorticoids, adrenal extract supplements, etc.) that could complicate medical management or compromise participation in research.

The inclusion criterion for TE participants was that the individual consented to providing documentation of current enrollment in a community-based OAT program that used either methadone or buprenorphine/naloxone treatment for OUD. Documentation was verified by NIDA IRP staff before the individual's enrollment. TE cohort individuals were excluded if they met exclusion criteria 1, 3, or 4 listed previously.

Across both groups, chronic pain status was assessed by asking the following questions: 1) "In the past 3 months, have you experienced any pain other than pain from opiate withdrawal?" and 2) "Is this pain constant or does it flare up frequently?" OBOT and TE participants who answered yes to both items were considered to have chronic pain (OUD+CP group). This approach is consistent with the minimal threshold for the International Association for the Study of Pain (IASP) classification of chronic pain [30]. The 3-month recall was chosen to reproduce Dunn et al's [19] characterization of chronic pain in patients with OUD on OAT and thus permits comparisons across studies.

Procedures

OBOT participants were enrolled in a 30-week office-based buprenorphine treatment program at the NIDA Archway Clinic, an outpatient research clinic. Participants completed twice-weekly toxicology screenings to corroborate self-reported substance use. TE participants were actively participating in either a methadone or buprenorphine treatment program at a community clinic during their enrollment in the parent project's monitoring study. Over a maximum period of 8 weeks, TE participants attended three weekly study sessions at the NIDA IRP clinic. At each visit, toxicology screenings were taken and used to corroborate self-reported substance use. TE participants' methadone or buprenorphine dose was self-reported at the first visit.

All participants underwent an assessment visit in which questionnaires and the PRT were administered as described below. In addition to completing the baseline assessment visit, participants were also given a smartphone to complete brief surveys via EMA. EMA is a technique to collect information about individuals' real-time behaviors and experiences in their natural environments. Each smartphone was preprogrammed with experimenter-configurable software, which delivered fixed and random prompts for participants to complete brief surveys on their momentary levels of a variety of psychological and substance-related measures. Detailed information about EMA data collection methods has been reported in previous papers [27–29]. In the present study, we focused on momentary reports of general mood levels, the presence or absence of pleasurable events, and the participant's cognitive and emotional response to those events if they occurred (see below: State Reward Responsiveness). All assessments were conducted after at least 5 weeks on OAT in the OBOT group. TE participants' treatment duration data were not available.

Measures

Behavioral Reward Responsiveness

The PRT [2], a laboratory-based task grounded within signal detection theory, assesses an individual's ability to modulate behavior on the basis of rewards. Participants completed three 100-trial blocks in which they were asked to discriminate between two perceptually similar stimuli. For the stimuli, a schematic face with no mouth (diameter: 25 mm; eyes: 7 mm) was first presented in the center of a 15-inch monitor. After a brief delay (500 ms), a straight line appeared as the mouth on the schematic face. Participants were instructed to choose whether the line represented a "little mouth" (i.e., 10.0 mm line) or a "big mouth" (i.e., 11.0 mm line) across trials. Line sizes were presented at equal frequencies throughout the task. To submit responses, participants pressed either the "v" or the "m" key on a computer keyboard, with the mouth/key associations randomly varying across participants counterbalanced across administrations. On a portion of correct trials, participants received a monetary reward with the feedback, "Correct!! You won 10 cents." Without the participants' knowledge, mouth lengths were randomly designated as either "rich" or "lean" stimuli, so that correct identification of rich stimuli were rewarded three times more frequently than correct identification of "lean" stimuli (i.e., 30 vs. 10 per block), resulting in an asymmetrical reinforcement schedule.

PRT data underwent a quality control assessment before subsequent analyses, consistent with prior studies [2, 31]. Trials were excluded if 1) the reaction time was <150 ms or $>1{,}500$ ms or 2) the reaction time value was above or below three standard deviations from the mean. To ensure adequate exposure to the asymmetrical reinforcement schedule, subjects displaying below chance ($<55\%$) accuracy and $>10\%$ outlier trials were excluded from analysis.

The primary outcome of interest for the PRT was response bias (RB), which is an index of reward responsiveness. RB measures the extent to which participants biased response patterns toward rich stimuli relative to lean stimuli. Consistent with previous work, RB in the present study was calculated as:

$$\text{Log } b = \tfrac{1}{2} \log \left[(\text{Rich}_{\text{correct}} * \text{Lean}_{\text{incorrect}})/(\text{Rich}_{\text{incorrect}} * \text{Lean}_{\text{correct}})\right]$$

The secondary outcome of interest was discriminability, which is an index of general task difficulty. Discriminability was calculated as:

$$\text{Log } d = \tfrac{1}{2} \text{ log } [(\text{Rich}_{\text{correct}} * \text{ Lean}_{\text{correct}})/\text{Rich}_{\text{incorrect}} * \text{ Lean}_{\text{incorrect}})]$$

Following prior procedures, RB and discriminability were computed by adding 0.5 to every cell in the matrix in the formula above [32].

Ecological Momentary Assessment of State Reward Responsiveness and Positive Mood

EMA was completed daily over the entire study period for each participant (i.e., maximum 15 weeks for OBOT participants and maximum 8 weeks for TE participants), as described in prior work from the parent study [27–29]. It should be noted that participants received about 28 random and end-of-day prompts per week. They were required to respond to at least 82% of these prompts ($\geq$23) within 15 minutes as a condition of continued participation. Both state reward responsiveness and positive mood were assessed on average 2.8 times (standard deviation [SD] = 0.61) daily via random prompts on a smartphone. Data quality was controlled by range limits on responses (i.e., participants could not respond outside the range of the scale). The study team met with each participant weekly to review the results of EMA compliance. If the participant's compliance did not meet the compliance threshold for 2 consecutive weeks despite the weekly reminder, he or she was discharged from the study. One participant in OBOT and two participants in TE were discharged. EMA compliance was further promoted through extensive training and providing small incentives. These resulted in a very high EMA compliance rate in the present study. Of a total 8,574 random prompts sent out during the study period, participants completed 8,460 (98.7%). More specifically, participants in the OBOT group completed a mean of 308 random prompts during the 15-week assessment period (SD = 34; min = 243; max = 338), and those in the TE group completed a mean of 145 random prompts during the 8-week assessment period (SD = 37; min = 42; max = 224). As the EMA compliance was very high, we conducted analyses based on the full number of participants.

For *state reward responsiveness*, at each randomly prompted entry, participants were asked to indicate whether or not (binary yes/no) they had recently experienced a pleasurable event not related to drug use. Individuals with affirmative responses were further asked to indicate the degree of pleasure experienced from this event (1 = "none" to 5 = "an extreme amount") and his/her intention to continue engaging in the event (1 = "none" to 5 = "the highest amount possible") on a five-point Likert scale. Among the completed random prompts, 904 (9.1%) were indicated as "yes" in experiencing a pleasurable event. Note that to increase the measurement reliability, especially given the low base rate of experiencing a pleasurable event, the random prompt assessments of state reward responsiveness were aggregated (averaged) at the day level.

Positive mood was separately assessed with seven adjectives (i.e., carefree, happy, lively, cheerful, relaxed, contented, and pleased) based on a factor analysis we conducted previously [28]. At each randomly prompted entry, participants were asked to rate the intensity with which they felt each adjective "just before the phone beeped," using a scale ranging from 1 (not at all) to 5 (extremely). Responses for the seven items were averaged into a positive mood score. The positive mood rating was not linked to the pleasurable event report. Then, random prompt assessments of positive mood were aggregated (averaged) at the day level. Note that the positive mood ratings were logged whether or not a pleasurable event was recorded.

Depressive Symptoms

Symptoms of depression were assessed with the Center for Epidemiological Studies–Depression (CES-D) [33] scale. Using a four-point Likert scale (1 = "less than 1 day," 4 = "5–6 days"), participants provided ratings for 20 items about their frequency of experiencing depressive symptoms over the prior week. Scores could range from 0 to 60; higher scores reflect endorsement of more severe depressive symptoms. This measure was included in analyses as a confounder.

Pain Severity and Interference

The Brief Pain Inventory (BPI) [34] was used to assess average pain severity over the previous 24 hours on scale of 0–10, where 0 = "no pain" and 10 = "pain as bad as you can imagine." We modified the questions on the BPI to ensure that participants reported on pain not related to opioid withdrawal. Additionally, the seven-item Pain Interference subscale of the BPI assessed the degree to which pain interfered with daily functioning over the previous 24 hours. This measure was included for descriptive purposes.

Data Analysis

Mixed-effects models were used to evaluate main and interaction effects for performance on the PRT. On the task, reward responsiveness was gauged by the rate of change in RB across the three blocks. As such, we modeled a random intercept to account for random variation in RB at Block 1. Within each pain group (OUD vs. OUD+CP), the *Block* main effect reflected the linear change in reward responsiveness (i.e., RB) across blocks. Evidence of group differences in reward responsiveness was evaluated with the *Pain Group* × *Block* interaction term. The evaluation of change across blocks is consistent with prior studies examining RB from the PRT [31, 35, 36]. Models described above were fit with depressive

symptoms (CES-D total score) and discriminability (i.e., an index of general task difficulty unrelated to reward, averaged across the second and third blocks after initial learning should have been acquired) as covariates. These covariates were included because depression is associated with reduced reward responsiveness on the PRT [31], and covarying discriminability controls for task difficulty.

Mixed-effects models were used to evaluate group differences in the state reward responsiveness index in the EMA, as observations were nested within persons. Momentary ratings of positive mood were averaged at the level of the day. Similarly, momentary ratings of pleasurable event responses (both pleasurable response rating and intent to continue) were averaged at level of the day. Hence, the two-level (i.e., level 1 = within-person level and level 2 = between-person level) mixed-effects modeling was conducted. The mixed-effect models included random intercepts, along with a fixed effect (i.e., *Pain Group*) that tested group differences. Random slope was not considered, as the models include only a level 2 (between-person) predictor. No covariate was included in the model, and the unstructured covariance matrix was used.

Results

Participants

Sample characteristics are provided in Table 1. The groups did not significantly differ in any demographic feature, and the distribution of OAT type was not significantly different between groups. The OUD+CP group had significantly greater pain severity ($t = -4.67$, $P < 0.001$, 95% confidence interval [CI]: –4.18 to –1.66) and pain interference ($t = -4.15$, $P < 0.001$, 95% CI: –4.88 to –1.69) on the BPI than that of the OUD group.

Table 1. Comparison of demographic and clinical characteristics

	OUD (n = 28)	OUD+CP (n = 19)
Demographic characteristics		
Sex, n		
Women	20	15
Men	8	4
Race, n		
Black	15	8
White	11	11
More than one race	1	0
Unknown	1	0
Ethnicity, n		
Hispanic	1	0
Non-Hispanic	26	19
Unknown	1	0
Age		
Mean age, y	47.5 ± 10.0	50.5 ± 8.3
Educational level, n		
Some high school	2	2
High school diploma	9	3
GED	12	6
Some college	5	6
College graduate	0	2
Clinical characteristics		
Clinical pain		
BPI severity	1.8 ± 2.0	4.68 ± 2.2
BPI interference	1.9 ± 2.5	5.1 ± 2.8
Medication		
Methadone, n	14	7
Dose, mg	80.00 ± 34.70	74.00 ± 30.91
Buprenorphine, n	14	12
Dose, mg	15.00 ± 4.28	14.53 ± 6.20
% of sample with positive opioid urine	39.46 ± 38.00	36.39 ± 39.05
% of sample with positive illicit drug urine (cannabis, amphetamine, cocaine, benzodiazepine, barbiturate, and PCP)	50.32 ± 43.81	36.28 ± 39.46
CES-D	12.5 ± 9.1	12.8 ± 6.2

Tests of Reward RB Differences Between Groups

As shown in Figure 1, there was a large main effect of *Block* in the OUD group ($B = 0.06$, standard error [SE] = 0.02, $t = 3.92$, $P < 0.001$, 95% CI: 0.03 to 0.09), reflective of an 83% increase in RB from Block 1 (mean = 0.14, SD = 0.12) to Block 3 (mean = 0.25, SD = 0.18). In contrast, the main effect of *Block* in the OUD+CP group was positive but not statistically significant ($B = 0.03$, SE = 0.02, $t = 1.90$, $P = 0.07$, 95% CI: –0.002 to 0.07), reflective of a 58% increase in RB from Block 1 (mean = 0.11, SD = 0.13) to Block 3 (mean = 0.17, SD = 0.14). In a separate model, we added the *Group* × *Block* interaction, which was not statistically significant ($B = 0.03$, SE = 0.02, $t = 1.21$, $P = 0.23$, 95% CI: –0.02 to 0.07).

Post hoc comparisons showed that groups did not differ in RB at Block 1 ($B = 0.03$, SE = 0.04, $t = 0.81$, $P = 0.42$, 95% CI: –0.05 to 0.11) or Block 2 ($B = 0.05$, SE = 0.04, $t = 1.31$, $P = 0.20$, 95% CI: –0.03 to 0.15) but did significantly differ at Block 3 ($B = 0.10$, SE = 0.05, $t = 2.08$, $P = 0.04$, 95% CI: 0.003 to 0.20), with the OUD group showing a larger RB at Block 3 than the OUD+CP group. This suggests that group differences in reward RB were strongest during the late, relative to the initial, acquisition phase.

Test of State Reward Responsiveness Differences Between Groups

Finally, we investigated the extent to which individuals reported changes in pleasure in response to pleasurable events in daily life, the descriptive statistics of which are presented in Table 2. Across the sample, individuals reported an average of 0.20 (SD = 0.57) pleasurable events per day. The OUD and OUD+CP groups did not significantly differ in the daily rate of pleasurable events reported ($B = -0.08$, SE = 0.12, degrees of freedom [df] = 44.11, $P = 0.53$, 95% CI: –0.32 to 0.17). Groups did not differ in the magnitude of feeling pleasure

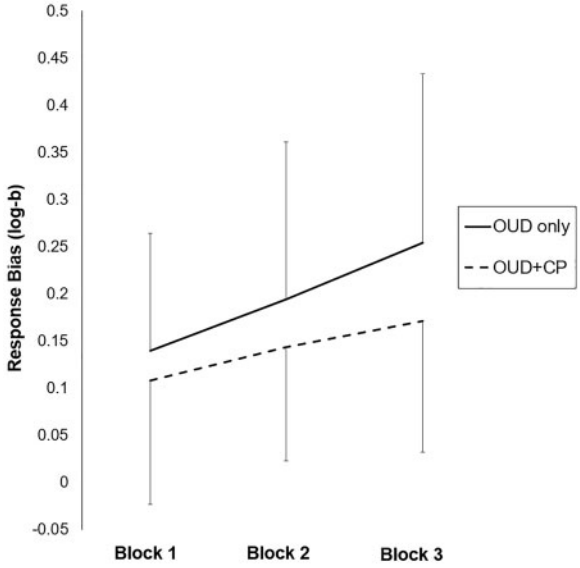

Figure 1. PRT RB in patients with OUD with and without chronic pain. RB (log-b) is plotted across blocks for OUD and OUD+CP groups. Error bars represent standard deviations from the mean. OUD RB mean ± SD: Block 1 = 0.14 ± 0.12, Block 2 = 0.19 ± 0.17, Block 3 = 0.25 ± 0.18. OUD+CP RB mean ± SD: Block 1 = 0.11 ± 0.13, Block 2 = 0.14 ± 0.12, Block 3 = 0.17 ± 0.14.

Table 2. Self-reported reward-related measures between groups

	OUD (Mean ± SD)	OUD+CP (Mean ± SD)	*P*
Daily rate of pleasurable events	0.21 ± 0.60	0.18 ± 0.52	0.27
Daily magnitude of pleasure response to pleasurable events	3.25 ± 0.74	3.14 ± 0.83	0.18
Daily intention to continue engaging in pleasurable events	3.20 ± 0.91	3.19 ± 0.95	0.88
Daily overall positive mood on days of pleasurable events	1.97 ± 0.55	2.06 ± 0.73	0.17

Bolded measures were the primary tests of subjective reward responsiveness.

reported on days in which at least one pleasurable event was reported ($B = -0.03$, SE = 0.16, df = 38, $P = 0.83$, 95% CI: –0.36 to 0.29). Groups also did not differ in the magnitude of intention to continue engaging in pleasurable activities on days in which at least one pleasurable event was reported ($B = 0.07$, SE = 0.20, df = 36.60, $P = 0.73$, 95% CI: –0.34 to 0.48).

As an additional check on the general positive mood, we also examined average levels of positive mood on days in which at least one (vs. zero) pleasurable event was reported. Across diary days in the full sample, average daily levels of positive mood were significantly higher on days in which at least one pleasurable event was reported than on days with zero pleasurable events were reported (at least one pleasurable event: mean = 2.00, SD = 0.62; zero pleasurable events: mean = 1.88, SD = 0.84; $B = 0.21$, SE = 0.04, df = 38.33, $P < 0.001$, 95% CI: 0.13 to 0.29]. However, groups did not differ in the average daily level of positive mood on days in which at least one pleasurable event was reported ($B = 0.10$, SE = 0.17, df = 39.59, $P = 0.54$, 95% CI: –0.23 to 0.44).

Discussion

The present study provided mixed evidence on the association of chronic pain with reduced reward responsiveness among individuals with OUD on OAT. First, whereas the OUD-only group evidenced robust reward responsiveness on the PRT, the OUD+CP group demonstrated reduced reward responsiveness, particularly in the late learning phase of the task. However, the groups did not statistically differ in the rate of reward RB across blocks or on state (EMA) measures of reward responsiveness. Overall, these results suggest that although there is a behavioral signal for a reward responsiveness deficit in patients with OUD+CP treated with OAT, it does not appear to translate into patients' responses to rewarding events as they unfold in daily life, as measured in the present study.

The present investigation was spurred by a growing body of literature that has revealed reward system dysfunction in patients with chronic pain [25, 37–42]. The OUD+CP group evidenced a weak and nonsignificant repeated-measures main effect of *Block* and had significantly lower RB than that of the OUD group at Block 3, when reward responsiveness was expected to be greatest. Several prior studies have demonstrated that performance on the PRT is associated with activation of the corticostriatal circuits [35, 43–45], a functionally interconnected group of brain regions responsible for the appraisal and valuation of rewarding stimuli. The corticostriatal circuits are heavily innervated with dopaminergic neurons, which are required for reinforcement and motivation [46]. Indeed, when phasic dopaminergic burst firing is pharmacologically blunted, healthy individuals demonstrate attenuated reward responsiveness on the PRT [47], similar to that observed in depressed individuals who have not undergone pharmacological manipulation [31]. Thus, performance on the PRT appears to be sensitive to person-level variation in dopaminergic neurotransmission. Against this background, our finding that patients with OUD+CP had attenuated reward RB on the PRT is consistent with the view that chronic pain may be a hypodopaminergic state [22, 24, 40].

Notably, the individuals with chronic pain in our study also had OUD. Like chronic pain, OUD is a chronic condition thought to gradually lead to functional deterioration of corticostriatal circuitry involved in reward processing [48]. The mechanisms underlying the "reward deficiency" syndrome in both OUD and chronic pain have been proposed to substantially overlap [49].

Recent evidence, however, suggests that OAT may re-regulate reward responsiveness in OUD [50]. The attenuated reward responsiveness observed in our OUD+CP sample may be a signal that chronic pain interferes with the putative reward re-regulation thought to be conferred by OAT, although the mixed findings across measures require cautious interpretation. There is a need for prospective studies to be conducted over a longer time course, and in a larger sample, to rigorously evaluate the question of how pain and reward interact in OUD. For example, we have very little understanding of *when* reward processing deficits (e.g., anhedonia) emerge in the course of the trajectory of chronic pain symptom development. Understanding how the confluence of chronic pain and OUD symptom trajectories influences reward processing over larger longitudinal time scales will be critical to prevention and treatment efforts. For example, outcomes of OAT, which commonly involves a combination of pharmacotherapy (e.g., methadone or buprenorphine) and supportive psychotherapy (e.g., cognitive-behavioral therapy), could be improved by tailoring to the needs of OUD subpopulations, such as those with OUD+CP [51].

Across groups, however, the pattern of the data generally supported those reported by Eikemo et al. [50], suggesting that patients with OUD maintained on methadone or buprenorphine did not show grossly dysfunctional behavioral or trait reward responsiveness. In the OUD group, the RB curve on the PRT was large and linear. Furthermore, even though the reward responsiveness curve of the OUD+CP group was 25% lower than that of the OUD group, the average increase in RB across blocks for OUD+CP was still 58%, suggesting that reward responsiveness may have been in the normal range. Thus, although the OUD+CP group evidenced quantitatively lower reward RB, particularly in the final block of the PRT, it may not be indicative of frank "dysfunction" of the reward system.

Although a prior study with a small sample has reported a correlation between behavioral and/or neurobiological reward measures and subjective measures of reward responsiveness [4], our results did not follow that pattern. The OUD and OUD+CP groups reported similar rates of pleasurable non-drug events and similar cognitive/affective responses to those events. Several factors may be at play in the discordance between task data and state self-report data, including reliability differences between measures and differences in response processes (e.g., perception vs. performance) [26]. Whereas the PRT incentivized correct responses with small monetary rewards, the events sampled in the random prompts of the EMA pertained to an array of potentially pleasurable life events that likely had little resemblance to receiving money. Additionally, our sample size was small, and replication in a larger sample is clearly needed to confirm the validity of the present findings. It is possible that learning rates for monetary rewards do not closely reflect how individuals with OUD and OUD+CP process naturalistic pleasurable events. Alternatively, it could be that the magnitude of effect on the PRT needs to be much greater to observe group differences in related naturalistic processes. Finally, null EMA findings may have been influenced by the extremely low volume of pleasant events reported (mean = 0.2 events/day), a finding at odds with other reports of positive events in OUD samples [52]. Methodological decisions related to sampling frequency and recall instructions may have influenced the narrow variance in pleasant event frequency that we observed; events were recorded at the momentary level (e.g., past 5 minutes), and it is possible that if we had chosen wider bands for retrospective reporting, a larger frequency of pleasant events would have been observed, and our EMA analyses might have yielded different results.

There were a few limitations of the present study that should be addressed in future work. First, the sample size was small and may have contributed to unstable estimates of group comparisons. The study may have lacked power to observe less than large between-group differences, so the present findings should be considered preliminary and their value assessed principally in their propensity to fuel future research. Second, because a substantial portion of the sample (73.2%) was recruited from community OAT clinics, we were unable to examine the role of specific treatment-related information (e.g., dose, time in treatment) on group differences. Third, we lacked physician confirmation of participants' self-reports of chronic pain and did not include a detailed assessment of chronicity beyond 3 months. Thus, although participants in the OUD+CP group reported "constant or frequently flaring" pain over at least 3 months, we lacked more detailed evaluation of their pain complaints. Fourth, we did not include a measure of pain severity during participants' performance on the PRT, so we were unable to evaluate the effects of acute pain on PRT performance. Interestingly, pain interferes with cognitive task performance in some individuals, whereas in other individuals, performance of a cognitive task is enhanced during acute pain [53, 54]. Thus, the lack of acute pain reports during the task is a potential limitation in that it could have biased performance in one direction or the other. However, if groups were systematically different in performance, we would have expected to see differences in the discriminability parameter in addition to the RB; the nonsignificant between-groups test of differences in discriminability argues against any systematic performance bias that may have influenced reward RB. Future studies could build upon this work by targeting specific comorbid pain disorders and conducting more thorough pain phenotyping. A final limitation is that, although we controlled for depressive symptoms in primary analyses of the PRT, individuals with current major depressive disorder were excluded from the study. Because depression is prevalent among patients with both OUD and chronic pain, the PRT data from this

study may not generalize to the broader population with OUD+CP.

Conclusions

This study set out to evaluate the degree to which chronic pain altered reward responsiveness and subjective reward responsiveness in patients with OUD maintained on either methadone or buprenorphine. We found a modest signal for attenuated reward responsiveness in patients with OUD+CP but not in OUD-only patients, suggesting that patients with OUD+CP may be challenged in their ability to incorporate and act on information to increase their chance of receiving rewards. However, the OUD and OUD+CP groups did not differ in subjective measures of state reward responsiveness, which raises questions about the robustness of the behavioral findings. Longitudinal studies with larger samples are necessary if we are to better understand the potential impact of chronic pain on reward responsiveness in patients with OUD.

References

1. Berridge KC. Reward learning: Reinforcement, incentives, and expectations. Psychol Learn Motiv 2000;40:223–78.
2. Pizzagalli DA, Jahn AL, O'Shea JP. Toward an objective characterization of an anhedonic phenotype: A signal-detection approach. Biol Psychiatry 2005;57(4):319–27.
3. Bakker JM, Goossens L, Kumar P, et al. From laboratory to life: Associating brain reward processing with real-life motivated behaviour and symptoms of depression in non-help-seeking young adults. Psychol Med 2019;49(14):2441–51.
4. Kasanova Z, Ceccarini J, Frank MJ, et al. Striatal dopaminergic modulation of reinforcement learning predicts reward-oriented behavior in daily life. Biol Psychol 2017;127:1–9.
5. Carver CS, White TL. Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: The BIS/BAS scales. J Pers Soc Psychol 1994;67 (2):319–33.
6. Flagel SB, Clark JJ, Robinson TE, et al. A selective role for dopamine in stimulus–reward learning. Nature 2011;469 (7328):53–7.
7. Zald DH, Boileau I, El-Dearedy W, et al. Dopamine transmission in the human striatum during monetary reward tasks. J Neurosci 2004;24(17):4105–12.
8. Pessiglione M, Seymour B, Flandin G, Dolan RJ, Frith CD. Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans. Nature 2006;442(7106):1042–5.
9. Aron A, Fisher H, Mashek DJ, et al. Reward, motivation, and emotion systems associated with early-stage intense romantic love. J Neurophysiol 2005;94(1):327–37.
10. Small DM, Jones-Gotman M, Dagher A. Feeding-induced dopamine release in dorsal striatum correlates with meal pleasantness ratings in healthy human volunteers. Neuroimage 2003;19 (4):1709–15.
11. Stice E, Spoor S, Bohon C, Veldhuizen MG, Small DM. Relation of reward from food intake and anticipated food intake to obesity: A functional magnetic resonance imaging study. J Abnorm Psychol 2008;117(4):924–35.
12. Wise RA, Leone P, Rivest R, Leeb K. Elevations of nucleus accumbens dopamine and DOPAC levels during intravenous heroin self-administration. Synapse 1995;21(2):140–8.
13. Koob GF, Le Moal M. Plasticity of reward neurocircuitry and the 'dark side' of drug addiction. Nat Neurosci 2005;8 (11):1442–4.
14. Koob GF, Volkow ND. Neurocircuitry of addiction. Neuropsychopharmacology 2010;35(1):217–38.
15. Burns JA, Kroll DS, Feldman DE, et al. Molecular imaging of opioid and dopamine systems: Insights into the pharmacogenetics of opioid use disorders. Front Psychiatry 2019;10:626.
16. Kiluk BD, Yip SW, DeVito EE, Carroll KM, Sofuoglu M. Anhedonia as a key clinical feature in the maintenance and treatment of opioid use disorder. Clin Psychol Sci 2019;7 (6):1190–206.
17. Hser Y-I, Mooney LJ, Saxon AJ, et al. Chronic pain among patients with opioid use disorder: Results from electronic health records data. J Subst Abuse Treat 2017;77:26–30.
18. Dunn KE, Brooner RK, Clark MR. Severity and interference of chronic pain in methadone-maintained outpatients. Pain Med 2014;15(9):1540–8.
19. Dunn KE, Finan PH, Tompkins DA, Fingerhood M, Strain EC. Characterizing pain and associated coping strategies in methadone and buprenorphine-maintained patients. Drug Alcohol Depend 2015;157:143–9.
20. Barry DT, Cutter CJ, Beitel M, et al. Psychiatric disorders among patients seeking treatment for co-occurring chronic pain and opioid use disorder. J Clin Psychiatry 2016;77(10):1413–9.
21. Tsui JI, Lira MC, Cheng DM, et al. Chronic pain, craving, and illicit opioid use among patients receiving opioid agonist therapy. Drug Alcohol Depend 2016;166:26–31.
22. Borsook D, Linnman C, Faria V, et al. Reward deficiency and anti-reward in pain chronification. Neurosci Biobehav Rev 2016;68:282–97.
23. Mitsi V, Zachariou V. Modulation of pain, nociception, and analgesia by the brain reward center. Neuroscience 2016;338 :81–92.
24. Taylor AM, Becker S, Schweinhardt P, Cahill C. Mesolimbic dopamine signaling in acute and chronic pain: Implications for motivation, analgesia, and addiction. Pain 2016;157(6):1194–8.
25. Elvemo N, Landrø NI, Borchgrevink PC, Håberg A. Reward responsiveness in patients with chronic pain. Eur J Pain 2015;19 (10):1537–43.
26. Dang J, King KM, Inzlicht M. Why are self-report and behavioral measures weakly correlated? Trends Cogn Sci 2020;24 (4):267–9.
27. Finan PH, Mun CJ, Epstein DH, et al. Multimodal assessment of sleep in men and women during treatment for opioid use disorder. Drug Alcohol Depend 2020;207:107698.
28. Preston KL, Kowalczyk WJ, Phillips KA, et al. Before and after: Craving, mood, and background stress in the hours surrounding drug use and stressful events in patients with opioid-use disorder. Psychopharmacology (Berl) 2018;235(9):2713–23.
29. Furnari M, Epstein DH, Phillips KA, et al. Some of the people, some of the time: Field evidence for associations and dissociations between stress and drug use. Psychopharmacology (Berl) 2015;232(19):3529–37.
30. Treede R-D, Rief W, Barke A, et al. Chronic pain as a symptom or a disease: The IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). Pain 2019;160 (1):19–27.
31. Pizzagalli DA, Iosifescu D, Hallett LA, Ratner KG, Fava M. Reduced hedonic capacity in major depressive disorder: Evidence from a probabilistic reward task. J Psychiatr Res 2008; 43(1):76–87.

32. Hautus MJ. Corrections for extreme proportions and their biasing effects on estimated values ofd′. Behav Res Methods Instrum Comput 1995;27(1):46–51.
33. Radloff LS. The CES-D scale: A self-report depression scale for research in the general population. Appl Psychol Meas 1977;1 (3):385–401.
34. Cleeland CS, Ryan K. The Brief Pain Inventory; 1994. Available at: https://www mdanderson org/education-andresearch/departments-programs-and-labs/departments-and-divisions/symptom-research/symptomassessment-tools/BPI_UserGuide.pdf (accessed March 1, 2016).
35. Kaiser RH, Treadway MT, Wooten DW, et al. Frontostriatal and dopamine markers of individual differences in reinforcement learning: A multi-modal investigation. Cereb Cortex 2018;28(12):4281–90.
36. Vrieze E, Pizzagalli DA, Demyttenaere K, et al. Reduced reward learning predicts outcome in major depressive disorder. Biol Psychiatry 2013;73(7):639–45.
37. Wood PB. Role of central dopamine in pain and analgesia. Expert Rev Neurother 2008;8(5):781–97.
38. Wood PB, Schweinhardt P, Jaeger E, et al. Fibromyalgia patients show an abnormal dopamine response to pain. Eur J Neurosci 2007;25(12):3576–82.
39. Nees F, Becker S, Millenet S, et al.; The IMAGEN Consortium. Brain substrates of reward processing and the mu-opioid receptor: A pathway into pain? Pain 2017;158(2):212–9.
40. Kim M, Mawla I, Albrecht DS, et al. Striatal hypofunction as a neural correlate of mood alterations in chronic pain patients. Neuroimage 2020;211:116656.
41. Martucci KT, Borg N, MacNiven KH, Knutson B, Mackey SC. Altered prefrontal correlates of monetary anticipation and outcome in chronic pain. Pain 2018;159(8):1494–507.
42. Seixas D, Palace J, Tracey I. Chronic pain disrupts the reward circuitry in multiple sclerosis. Eur J Neurosci 2016;44(3):1928–34.
43. Vrieze E, Ceccarini J, Pizzagalli DA, et al. Measuring extrastriatal dopamine release during a reward learning task. Hum Brain Mapp 2013;34(3):575–86.
44. Whitton AE, Kakani P, Foti D, et al. Blunted neural responses to reward in remitted major depression: A high-density event-related potential study. Biol Psychiatry 2016;1(1):87–95.
45. Santesso DL, Dillon DG, Birk JL, et al. Individual differences in reinforcement learning: Behavioral, electrophysiological, and neuroimaging correlates. Neuroimage 2008;42(2):807–16.
46. Palmiter RD. Dopamine signaling in the dorsal striatum is essential for motivated behaviors: Lessons from dopamine-deficient mice. Ann N Y Acad Sci 2008;1129(1):35–46.
47. Pizzagalli DA, Evins AE, Schetter EC, et al. Single dose of a dopamine agonist impairs reinforcement learning in humans: Behavioral evidence from a laboratory-based measure of reward responsiveness. Psychopharmacology (Berl). 2008;196 (2):221–32.
48. Moningka H, Lichenstein S, Yip SW. Current understanding of the neurobiology of opioid use disorder: An overview. Curr Behav Neurosci Rep 2019;6(1):1–11.
49. Elman I, Borsook D. Common brain mechanisms of chronic pain and addiction. Neuron 2016;89(1):11–36.
50. Eikemo M, Lobmaier PP, Pedersen ML, et al. Intact responses to non-drug rewards in long-term opioid maintenance treatment. Neuropsychopharmacology 2019;44 (8):1456–63.
51. Barry DT, Beitel M, Cutter CJ, et al. An evaluation of the feasibility, acceptability, and preliminary efficacy of cognitive-behavioral therapy for opioid use disorder and chronic pain. Drug Alcohol Depend 2019;194:460–7.
52. Knapp KS, Bunce SC, Brick TR, Deneke E, Cleveland HH. Daily associations among craving, affect, and social interactions in the lives of patients during residential opioid use disorder treatment. Psychol Addict Behav 2020 (doi: 10.1037/adb0000612).
53. Seminowicz D, Mikulis D, Davis K. Cognitive modulation of pain-related brain responses depends on behavioral strategy. Pain 2004;112(1):48–58.
54. Erpelding N, Davis KD. Neural underpinnings of behavioural strategies that prioritize either cognitive task performance or pain. Pain 2013;154(10):2060–71.