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Increased neural activity in the right dorsolateral prefrontal cortex during a risky decision-making task is associated with cocaine use in methadone-maintained patients

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Abstract

Background—Methadone maintenance is an effective treatment for opioid use disorder (OUD), yet many methadone-maintained patients (MMPs) struggle with cocaine use during OUD recovery. The current study aimed to identify whether prefrontal cortex (PFC) activity during a risky decision-making task was associated with cocaine use during a 90-day follow-up in MMPs.

Methods—MMPs (N=28) attended a single neuroimaging session wherein PFC activity was measured using functional near-infrared spectroscopy (fNIRS) during the Balloon Analogue Risk Task (BART). Trait impulsivity was assessed via the Barratt Impulsiveness Scale version 11 (BIS-11). Following the neuroimaging session, MMPs were tracked via electronic health records for 90 days to determine treatment outcomes including cocaine use verified by urine drug screens.

Results—During the BART, MMPs who used cocaine displayed increased neural activity in the right PFC during active decision-making ($F_{1, 22}$=14.75, p=0.001) and the right dorsolateral PFC during active minus passive decision-making ($F_{1, 22}$=5.56, p=0.028) compared to participants who did not use cocaine. Receiver operating characteristic curves confirmed that neural activity in the right PFC during active decision-making (AUC=0.841, 95% CI, 0.697–0.985, p=002), and in the

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Contributors

This research was designed by ASH, RKB, and KED. All authors contributed to the manuscript preparation. ASH performed all data analyses. All authors read and approved the final manuscript.

right dorsolateral PFC during active minus passive decision-making (AUC=0.805, 95% CI, 0.643–0.968, p=0.006) was associated with continued cocaine use. MMPs who used cocaine versus those who did not reported increased trait impulsivity on the BIS-11 Total Score (t=−2.28, p=0.031).

Conclusions—The fNIRS device is portable, relatively easy to use, and potentially feasible for use in methadone outpatient programs to assess propensity for negative treatment outcomes such as continued cocaine use.

Keywords

Opioid Use Disorder; Methadone; Cocaine Use; Neuroimaging; Functional Near-Infrared Spectroscopy; Treatment Outcomes

1. Introduction

Methadone maintenance is a mainstay for opioid use disorder (OUD) treatment, with more than 350,000 Americans utilizing methadone in 2015 (Alderks, 2017). Although methadone maintenance is effective in reducing illicit opioid use (Sees et al., 2000), many methadone-maintained patients (MMPs) have co-occurring substance use disorders (SUDs) that often go unchecked (Brooner et al., 1997). Indeed, cocaine use is common among MMPs (Kolar et al., 1990; Condelli et al., 1991; Dobler-Mikola et al., 2005), yet cocaine use has proven difficult to treat in this population and is often associated with poor clinical outcomes (Schottenfeld et al., 2005; Williamson et al., 2006; Peirce et al., 2006; Carroll et al., 2014). Apart from cocaine-positive urine drug screens that provide a limited point-in-time measure of abstinence or use, there are no biological measures that prospectively identify which MMPs might use cocaine during OUD recovery.

The biological underpinnings of impulsive behaviors may contribute to cocaine use during methadone maintenance. Trait impulsivity is broadly associated with SUDs (De Wit, 2009), and is especially pronounced in those who use cocaine (Monterosso et al., 2001)(García-Marchena et al., 2018). From a neurobiological perspective, trait impulsivity has been associated with decreased executive function (Bechara, 2005) and decreased gray-matter volume in the prefrontal cortex (PFC) (Yip et al., 2018). The dorsolateral (DL)PFC, which exerts executive control over impulsive behaviors and allocation of attention (Goldstein and Volkow, 2011), is activated during tasks that require response inhibition in non-methadone-treated individuals with OUD (Fu et al., 2008), and increased DLPFC activity in methadone- and buprenorphine-maintained individuals might be compensatory for diminished behavioral control during decision-making tasks (Yücel et al., 2007).

Very few neuroimaging studies have examined the neural correlates associated with cocaine use in MMPs (Yip et al., 2016; Moningka et al., 2018; DeVito et al., 2019), and there is no published neuroimaging research comparing MMPs with and without cocaine use. The current study administered the Balloon Analogue Risk Task (BART), a well-established risky decision-making paradigm that models real-world risk/reward escalation (Lejuez et al., 2002), during functional near-infrared spectroscopy (fNIRS) imaging to assess the PFC correlates associated with continued cocaine and illicit opioid use during a 90-day follow-up in MMPs. We hypothesized that increased neural activity in the DLPFC during the decision-

making portion of the BART would be associated with cocaine and opioid use during the 90-day follow-up.

2. Methods

2.1 Participants

Participants in this study were part of another sample that examined the relationship between drug-cue reactivity and continued illicit opioid use (Huhn et al., 2019). Of the 30 participants recruited, two participants were excluded for excessive head motion during the fNIRS-BART paradigm, resulting in a study sample of N=28. Participants were included in the study if they were (1) enrolled in methadone-maintenance treatment for OUD, (2) 18 or older, (3) right-handed, (4) able to pass an intoxication test at the time of their methadone dose and study session, and (5) in treatment between 3-weeks and 18-months. Exclusion criteria included (1) any major psychiatric condition, psychotic features, or dementia, or (2) a significant clinical problem that would compromise patient care. The Johns Hopkins Institutional Review Board approved the study protocol and all participants provided informed consent to participate.

2.2 Design

Participants were scheduled for a single study visit that began immediately after methadone dosing and lasted approximately three hours. During the visit, participants completed demographic questionnaires, the Barratt Impulsiveness Scale version 11 (BIS-11) (Patton and Stanford, 1995), and the Addiction Severity Index (ASI) (McLellan et al., 1997). fNIRS imaging began approximately two hours after methadone dosing, corresponding to peak effects of methadone (Dale et al., 2004), and ensuring experimental control over the acute effects of methadone dosing during the fNIRS paradigm (Langleben et al., 2008).

2.3 Balloon Analogue Risk Task (BART)

The BART was modified in MatLab™ (The Mathworks, Inc., Sherborn, MA) for use with an fNIRS system (fNIR Devices, LLC; Potomac, MD) (Cazzell et al., 2012). The BART paradigm included two conditions: an active condition wherein the participant actively pumped the balloon, and a passive condition wherein the computer had control of the balloon (no active pumping). The fNIRS-BART protocol used in this study was consistent with previous studies (Rao et al., 2008; Cazzell et al., 2012) regarding risk of popping, actual probability of popping, value of winnings (wager), and reward variance.

Resting state PFC signal was recorded for 60 seconds prior to initiation of the BART to establish baseline measurements. Both passive and active conditions were counterbalanced and consisted of 20 trials that began when the participant initiated inflation of the balloon. In the passive condition, the program took control over pumping the balloon (one second off-time between pumps), and participants passively viewed the escalating risk/reward proposition. In the active condition, participants actively pumped the balloon, waiting 1–2 seconds between pumps. The end of each trial was marked by either the balloon popping with the prompt “You Lose!”, or the participant choosing to stop and thus gaining virtual

reward for the trial with the prompt “You Win!”. Participants had a 15-second recovery period after each trial.

This study utilized a block design to examine the PFC-correlates of decision-making during the BART. The decision-making portion of the task was defined as the time period between the first and last pump of each trial. In each condition (active or passive), neuroimaging data was analyzed separately for decision-making that led to a win and decision-making that led to a loss.

Regional changes in PFC blood flow were measured via fNIRS detection of infrared light spectra for oxygenated and deoxygenated hemoglobin (Ferrari and Quaresima, 2012). In the current study, data were recorded using a continuous wave system (Model 1200, fNIR Devices, LLC, USA) and a pad containing 16 optodes (4 LED light sources and 10 photodetectors) and recorded data at 2Hz throughout the experimental protocol using COBI Studio (Ayaz et al., 2011). Head circumference was assessed for each participant and sensors were aligned at the bottom row of optodes with the International 10–20 sites F7, FP1, FP2, F8 line (Ayaz et al., 2006). This placement situated the sensor over bilateral rostral PFC and bilateral ventrolateral/DLPFC (Okamoto et al., 2004).

2.3.1 fNIRS Signal Processing—

fNIRS data processing used raw light intensity from 16 optodes with two wavelengths that were low-pass filtered with a finite impulse response, with a linear phase filter with order 20 and a cut-off frequency of 0.1 Hz (to attenuate high frequency noise, respiration, and cardiac cycle effects). All data were inspected for potential saturation (defined as light intensity at the detector being greater than the analog-to-digital converter limit) and motion artifact contamination by means of a coefficient of variation based assessment (Ayaz et al., 2010), and were corrected for motion artifacts. The final output of each optode was change from baseline, mean oxygenated hemoglobin (HbO_2) during blocks of time wherein decisions were being made (active condition) or viewed (passive condition). Within each participant, a mean decision-making score (change from baseline HbO_2) was calculated for each of the 16 optodes during active and passive decision-making that led to a win or loss of reward. Subsequently, results from the passive condition were subtracted from results from the active condition to isolate PCF regions involved in the active decision-making process. Increased or decreased hemodynamic flow was treated as a secondary marker of increased or decreased neural activity, respectively.

2.4 Treatment Outcomes

Continued cocaine and opioid use were the primary and secondary study outcomes, respectively, and were assessed weekly for 90 days following the fNIRS session as part of routine direct observation at the opioid treatment program. Cocaine and opioid use were treated as binary (any positive urine drug screen) and continuous (e.g., percent negative urine drug screens) variables. One patient who dropped out of treatment during that period was included in the analyses as having continued cocaine and opioid use because the patient had already tested positive for those substances during the 90-day follow-up. Baseline drug use was assessed via the ASI and confirmed from the results of routine urine analyses taken by the clinic in the four weeks leading up to the study session.

2.5 Data Analysis

Participants were dichotomized into groups consisting of No Cocaine Use (n=15) or Continued Cocaine Use (n=13) based upon provision of ≥1 cocaine-positive urine sample during the post-fNIRS 90-day follow-up period. Demographic and questionnaire data were then compared between the groups using independent student t-tests for continuous or Chi-square analyses for dichotomous variables. Given that days in treatment and years of education were significantly different between groups, and that years of cocaine use was marginally different but clinically relevant, all further primary treatment outcome analyses controlled for these variables; all reported study results were significant with and without inclusion of these covariates. Partial correlations controlling for days in treatment, years of education, and years of cocaine use were used to examine the association between BIS-trait impulsivity and percent negative cocaine or opioid drug screens. A one-way analysis of covariance was used to examine group differences in neural activity (measured via changes in hemodynamic flow) during the BART task. fNIRS data was considered significant if ≥3 adjacent optodes were each significantly different between groups at $p<0.05$; the conditional probability that these clusters would represent a Type 1 Error was 0.00013, which is less than the Bonferroni-adjusted p-value for a 16 optode fNIRS measure (0.00313). Mean values for each cluster were calculated and compared between groups. In addition to days in treatment, years of education, and years of cocaine use, number of inflations during each BART trial was included as a covariate to control for behavioral differences during the fNIRS-BART paradigm. Receiver operating characteristic (ROC) curves were then used to classify the proportion of individuals who did or did not use cocaine during the 90-day follow-up based on neuroimaging results that were significant between groups. An ROC curve for past 30-day cocaine use was also derived as a well-established predictor of future cocaine use (Lamb et al., 1996) that could be used as a benchmark for neuroimaging results. Finally, as an exploratory analysis, a discriminant function analysis with a leave-one-out cross validation was used to create a predictive model of cocaine use during the 90-day follow-up based on the strongest neuroimaging results coupled with past 30-day cocaine use. Alpha levels for all significant findings were set at $p<0.05$. Statistical analyses were conducted using SPSS version 24.0 (IBM, Armonk, NY).

3. Results

3.1 No Cocaine Use versus Continued Cocaine Use during Follow-up

Participants in this study (N=28) were 57.1% male, 85.7% white, and had a mean (SD) age of 42.1 (13.7) (Table 1). At baseline, 30.1% of participants who used cocaine during follow-up reported no cocaine use in the past 30 days, while 100% of participants who did not use cocaine during follow-up reported no cocaine use in the past 30 days. During the 90-day follow-up period, participants who used cocaine provided 65.2% cocaine positive and 30.6% opioid positive urine drug screens, while participants who did not use cocaine provided 5.0% opioid positive urine drug screens. Participants who used cocaine during follow-up had higher BIS-11 Total Scores compared to participants who did not use cocaine, however there were no differences in BART behavioral measures (Table 1). During the BART, participants who used cocaine during the follow-up period displayed increased neural activity in the right lateral PFC during baseline-corrected, active decision-making that led to a loss

($F_{1, 22}$=14.75, p=0.001), and in the right DLPFC during active minus passive decision-making that led to a loss ($F_{1, 22}$=5.56, p=0.028) compared to participants who did not use cocaine (Figure 1). There were no significant differences that met the *a priori* criteria for neural activity regarding decision-making that led to a win, nor were there differences in persons who did or did not use opioids during the 90-day follow-up.

ROC curve analyses classifying participants who did or did not use cocaine during the 90-day follow-up were significant for neural activity in the right lateral PFC during baseline-corrected, active decision-making that led to a loss (area-under-the-curve [AUC]=0.841, 95% confidence interval [CI], 0.697–0.985, p=002), in the right DLPFC during active minus passive decision-making that led to a loss (AUC=0.805, 95% CI, 0.643–0.968, p=0.006), and for past 30-day cocaine use (AUC=0.846, 95% CI, 0.685–1.00, p=0.002). Discriminant function analysis using both neural activity in the right lateral PFC during baseline-corrected, active decision-making that led to a loss *and* past 30-day cocaine use correctly classified 96.4% of participants who did or did not use cocaine during the 90-day follow-up (specificity = 100%, sensitivity = 92.3%; p<0.001); a leave-one-out cross validation analysis also correctly classified 96.4% of participants who did or did not use cocaine during the 90-day follow-up.

3.2 Correlations between Trait Impulsivity and Treatment Outcomes

Percent cocaine-negative urine drug screens during the 90-day follow-up period were marginally associated with the BIS-11 Total Score (r= −0.328, p=0.118), and significantly associated with the BIS-11 Attentional Subscale (r= −0.422, p=0.045). There was no significant correlation between BIS-11 Total Score and opioid-negative urines during the 90-day follow-up, nor was there a significant correlation between neural activity in the right DLPFC during the BART and BIS-11 Total Score.

4. Discussion

The current study utilized a novel approach to identify biological and subjective indicators of continued cocaine use in MMPs. The fNIRS-adapted BART paradigm detected a significant increase in the right PFC during behaviors that led to a loss of reward in MMPs who subsequently went on to use cocaine during the 90-day follow-up, versus those who did not. Subtracting the passive from the active condition of the BART suggested that the right DLPFC was involved in decision-making that that led to a loss of reward in MMPs who used cocaine during the 90-day follow-up versus those who did not. Given that recent cocaine use is a known risk-factor for future cocaine (Lamb et al., 1996), and past 30-day cocaine use was reported by a majority of patients who continued to use cocaine during the 90-day follow-up, the combination of fNIRS results and past 30-day cocaine use was explored via discriminant function analysis. It is noteworthy that 30.1% of participants who used cocaine during the 90-day follow-up did not report past 30-day cocaine use, and ROC curves for fNIRS results and past 30-day cocaine use were similar, both correctly classifying ~84% of MMPs who did or did not use cocaine during the 90-day follow-up. The exploratory discriminant function analysis that combined fNIRS results and past 30-day cocaine use correctly classified 96.4% of MMPs who did or did not use cocaine during the 90-day

follow-up; a leave-one-out cross validation also correctly classified 96.4% of MMPs, suggesting that the combination of PFC response to risky decision-making and self-reported drug use behaviors might create a robust predictive model to identify MMPs at high risk for continued cocaine use. At the same time, combining predictors in a relatively small sample could result in a model that is overfit, and future research will be necessary to examine the accuracy of predictive models that combine objective and subjective measures.

Whereas trait impulsivity was also significantly greater in MMPs who used cocaine during follow-up versus those who did not, these subjective measures were not correlated to neural activity, suggesting that the fNIRS-adapted BART paradigm is a unique index of cocaine use in this population that is not related to traditional self-report assessments. Moreover, the fNIRS device is economical and relatively easy to use, with ultra-portable versions that are wireless and battery operated (Ayaz et al., 2013; McKendrick et al., 2016). As such, this neuroimaging device could be readily deployed in addiction treatment programs to measure biological indicators of continued drug use or relapse risk that would not be subject to self-report bias. While this study is a promising first (and small) step in developing a clinic-friendly neuroimaging assay for continued cocaine use in MMPs, it is crucial that future fNIRS research be conducted in larger samples, and in trials aimed at prospectively identifying drug use to assess the clinical utility and confirm the reliability and reproducibility of this approach. Identifying neurobiological differences between MMPs with and without cocaine-use may also pave the way for development of novel treatments based on known brain mechanisms (Moningka et al., 2018), such as cognitive-behavioral approaches that directly address risky decision-making (McHugh et al., 2010; Carroll et al., 2014).

One prior study using a novel reward-related decision-making task reported decreased insula and inferior frontal gyrus (IFG) activity during the anticipation/decision-making phase preceding a loss event in MMPs compared to healthy controls (Gradin et al., 2014). Similarly, decreased IFG/DLPFC activity was also reported during loss anticipation among MMPs with co-occurring cocaine-use disorder, relative to both healthy controls and individuals with cocaine-use disorder who were not maintained on methadone (Yip et al., 2016). Neither of these studies included a methadone maintained, non-cocaine using comparison group. The current study extends this line of research by utilizing only MMPs and demonstrating that increased DLPFC activity during risky decision-making differentiated MMPs who used cocaine relative to those who did not during a 90-day follow-up. Future neuroimaging studies could examine three groups, including MMPs who do not use cocaine, MMPs who use cocaine, and non-MMPs who primarily use cocaine, to assess the nuances in the effects of combined or sole use of methadone and cocaine, respectively.

This study is limited by a small sample size of MMPs, although this is consistent with other neuroimaging studies in OUD patients (Yücel et al., 2007; Gradin et al., 2014; Yip et al., 2016). In addition, fNIRS lacks an anatomical scan, though the large area of interest supports reliance on optode placement. Another potential limitation of this study is the use of a block design with 1–2 seconds between decisions during the BART. The reliance on hemodynamic response as a secondary marker of neural activity prevented the event-related evaluation of specific ‘risky decisions’. Also, the fNIRS device utilized in this study had a

sampling rate of 2 Hz (similar to fMRI); future studies could utilize fNIRS devices with enhanced temporal resolution or electroencephalography during a behavioral task to further elucidate the neural correlates of risky decision-making associated with cocaine use in MMPs. In contrast to these limitations, use of fNIRS in this study is both novel and informative. While there is a need to replicate these findings in a larger sample, this technology could be readily deployed in addiction treatment centers, which often exist apart from academic medical centers and rarely have access to fMRI. The results of this study demonstrate that an fNIRS-adapted version of the BART reveals drug-specific neural differences in MMPs, differences which were not revealed from behavioral results of the BART. Thus, this neuroimaging paradigm might have clinical utility in objectively identifying unique risk for cocaine use, which is a major problem in methadone treatment programs.

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Conflict of Interest

HA was involved in the technology development of the brain-imaging instrument manufactured by fNIR Devices, LLC and owns a minor share of the firm. ASH receives research funding from Ashley Addiction Treatment through his university. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. There are no conflicts to report for RKB, MMS, SWY, or KED.

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Highlights

- Methadone patients often co-use other substances, such as cocaine.
- Prefrontal cortex activity during a decision-making task predicted cocaine use
- Increased trait impulsivity was associated with cocaine use during 90-day follow-up
- Functional near-infrared spectroscopy could be used to assess drug use outcomes

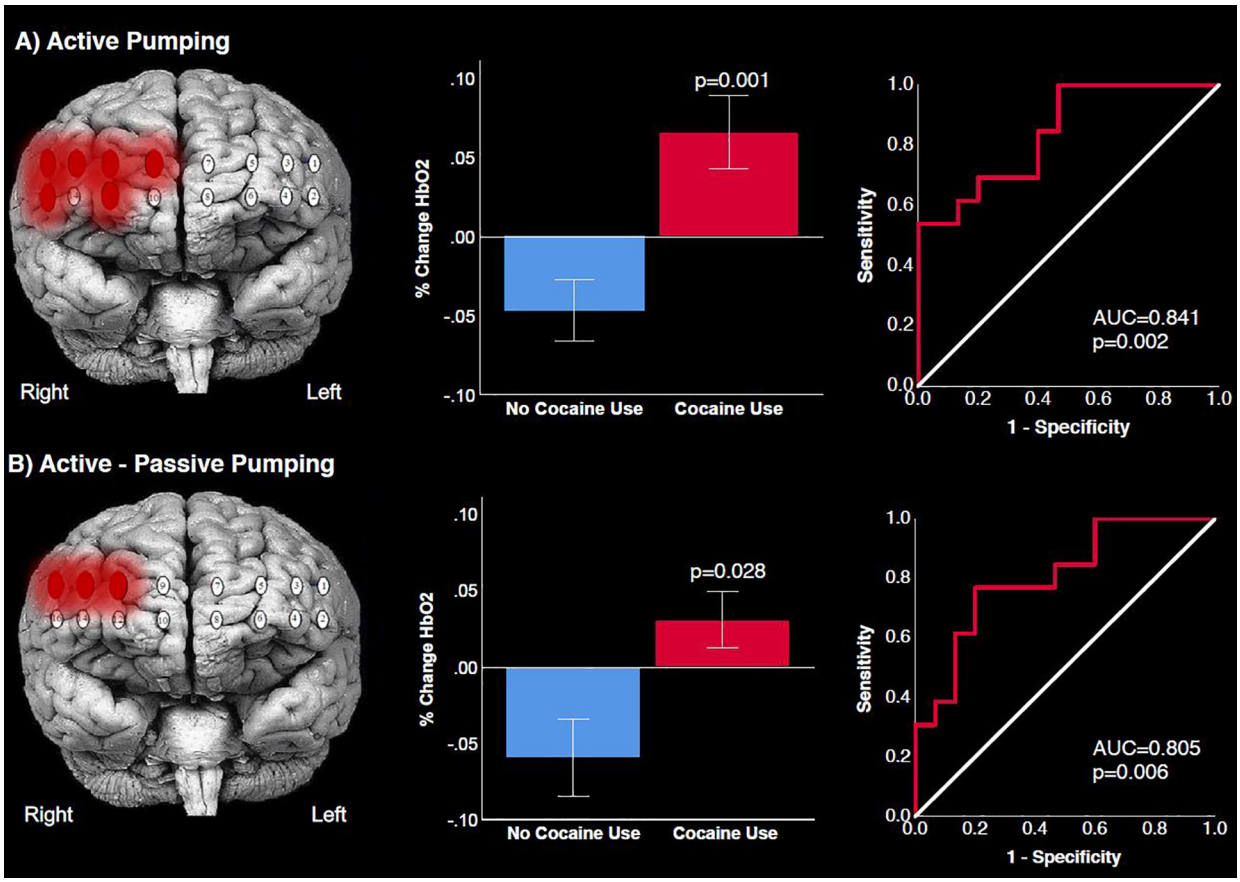

Figure 1.

Prefrontal cortex (PFC) activity during the Balloon Analogue Risk Task (BART) in patients who did (red) or did not (blue) use cocaine in the subsequent 90-day follow-up period. Mean (standard error) differences are displayed in bar graphs and receiver operating characteristic curves demonstrate area-under-the-curve (AUC) for correct classification. Top (A): Baseline corrected neural activity during decision-making that led to loss of reward on the BART. Bottom (B): To examine areas of the PFC responsible for decision making, independent of viewing the BART paradigm, passive decision-making (i.e. watching the program make decisions) was subtracted from active decision-making that led to loss of reward.

Table 1.

Baseline Participant Characteristics

		Grouped by Cocaine Use during 90-day Follow-up		
	Total Sample (N=28)	**Cocaine Abstinent (n=15)**	**Cocaine Use (n=13)**	**t or χ^2 (p-value)**
Age, M (SD)	42.1 (13.7)	42.9 (14.8)	41.3 (12.9)	0.29 (0.770)
Sex (% Male)	57.1	53.3	61.5	0.19 (0.662)
Race (% White)	85.7	86.6	84.6	0.02 (0.877)
Ethnicity (% Hispanic)	3.6	0.0	7.7	1.20 (0.274)
Years Education, M (SD)	12.4 (2.8)	13.7 (2.6)	10.8 (2.2)	**3.24 (0.003)**
Days Working in Past 30, Days M (SD)	9.4 (10.0)	9.2 (10.2)	9.6 (10.2)	−0.09 (0.929)
Living Situation (% Homeless)	7.1	0.0	15.4	2.49 (0.115)
Methadone Dose, milligrams, M (SD)	76.0 (23.4)	77.0 (24.8)	74.8 (22.5)	0.24 (0.812)
Days in Treatment, M (SD)	187.5 (184.8)	256.5 (201.9)	107.8 (128.3)	**2.28 (0.031)**
Lifetime Diagnosis Depression (%)	35.7	40.0	30.1	0.26 (0.611)
Past 30-day Drug Use M (SD)				
Heroin	2.5 (6.8)	0.1 (0.5)	5.2 (9.3)	−1.96 (0.073)
Prescription Opioids	0.6 (1.9)	0.5 (1.8)	0.8 (2.0)	−0.32 (0.749)
Cocaine	5.5 (10.3)	0.0 (0.0)	11.8 (12.6)	**−3.37 (0.006)**
Alcohol (to Intoxication)	0.5 (2.0)	0.1 (0.3)	1.1 (2.9)	−1.25 (0.234)
Benzodiazepines	0.4 (1.0)	0.1 (0.3)	0.7 (1.3)	−1.69 (0.116)
Lifetime Drug Use Years M (SD)				
Heroin	6.2 (8.1)	5.2 (7.7)	7.3 (8.6)	−.068 (0.501)
Prescription Opioids	6.9 (7.1)	7.7 (7.2)	6.0 (7.1)	0.61 (0.548)
Cocaine	3.4 (5.5)	1.6 (2.6)	5.4 (7.2)	−1.81 (0.090)
Alcohol (Problematic)	8.1 (13.0)	5.4 (9.8)	11.2 (15.7)	−1.12 (0.246)
Benzodiazepines	1.5 (3.1)	1.8 (3.5)	1.2 (2.8)	0.50 (0.618)
BIS-11 Total Score M (SD)	69.5 (11.5)	65.2 (9.6)	74.5 (11.8)	**−2.28 (0.031)**
Attention Subscore, M (SD)	16.9 (3.9)	15.2 (3.2)	18.6 (3.9)	**−2.49 (0.019)**
Motor Subscore, M (SD)	24.4 (4.0)	23.1 (3.7)	25.8 (4.0)	−1.80 (0.083)
Nonplanning Subscore, M (SD)	28.6 (5.4)	27.3 (4.8)	30.1 (6.0)	−1.39 (0.177)
Balloon Analogue Risk Task, Behavioral				
Total Wins, M (SD)	13.7 (2.7)	14.4 (2.3)	12.9 (2.9)	1.57 (0.128)
Total Reward, $, M (SD)	8.3 (2.8)	8.8 (3.2)	7.7 (2.1)	1.07 (0.295)
Adjusted Number of Inflations, M (SD)	4.9 (0.7)	4.9 (0.7)	5.0 (0.8)	−0.21 (0.837)

Baseline demographics, drug use behaviors (from the Addiction Severity Index), self-report/clinical assessments of depressive symptoms, and trait impulsivity in methadone maintained patients. All data in this table were collected on the day of the experimental session. Results are grouped by patients who did or did not use cocaine during the subsequent 90-day follow-up period. Group comparisons utilized independent t-tests for continuous variables and chi-squared for discrete variables. MMPs = methadone-maintained patients, M=mean, SD = standard deviation, BIS-11 = Barratt Impulsiveness Scale 11. Significant differences (p<.05 or lower) in **bold.**