**Drug and Alcohol Dependence**

# Impulsivity and craving in subjects with opioid use disorder on methadone maintenance treatment

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| **Abstract:** | Background: Methadone maintenance treatment (MMT) is effective in decreasing opioid use or facilitating abstinence. Previous studies using small opioid use disorder samples suggest that cognitive impairments including impulsivity and executive functions may partially improve on MMT, but a range of deficits may persist. However, systematic assessments with larger samples are needed to confirm the profile of cognitive functions on MMT.<br>Methods: We assessed four types of impulsivity (delay discounting, reflection impulsivity, risk taking and motoric impulsivity), executive functioning (spatial working memory, paired associative learning and strategic planning) and drug cue-induced craving in a relatively large population (115 MMT patients, 115 healthy controls). The relationships between impulsivity, drug cue-induced craving and addiction-related variables were also assessed.<br>Results: Delay discounting, as well as drug cue-induced craving was increased in patients, while motoric impulsivity was lower than in controls. Paired associative learning was additionally impaired, which was explained by increased depression and anxiety levels in patients. Within the MMT group, the delay discounting and drug-cue induced craving scores were positively correlated with self-reported urgency, but unrelated to methadone dosage, duration on methadone, withdrawal symptoms, or presence of nicotine dependence.<br>Conclusions: Our findings highlight increased delay discounting and cue-induced craving in MMT patients suggesting a potential role for trait effects in delay discounting. Although previous smaller studies have shown impaired executive function, in our large sample size on chronic MMT we only observed impaired associative learning related to depressive and anxiety symptoms highlighting a role for managing comorbid symptoms to further optimize cognitive function. |

# Impulsivity and craving in subjects with opioid use disorder on methadone maintenance treatment

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**Abstract**

**Background:** Methadone maintenance treatment (MMT) is effective in decreasing opioid use or facilitating abstinence. Previous studies using small opioid use disorder samples suggest that cognitive impairments including impulsivity and executive functions may partially improve on MMT, but a range of deficits may persist. However, systematic assessments with larger samples are needed to confirm the profile of cognitive functions on MMT.

**Methods:** We assessed four types of impulsivity (delay discounting, reflection impulsivity, risk taking and motoric impulsivity), executive functioning (spatial working memory, paired associative learning and strategic planning) and drug cue-induced craving in a relatively large population (115 MMT patients, 115 healthy controls). The relationships between impulsivity, drug cue-induced craving and addiction-related variables were also assessed.

**Results:** Delay discounting, as well as drug cue-induced craving was increased in patients, while motoric impulsivity was lower than in controls. Paired associative learning was additionally impaired, which was explained by increased depression and anxiety levels in patients. Within the MMT group, the delay discounting and drug-cue induced craving scores were positively correlated with self-reported urgency, but unrelated to methadone dosage, duration on methadone, withdrawal symptoms, or presence of nicotine dependence.

**Conclusions:** Our findings highlight increased delay discounting and cue-induced craving in MMT patients suggesting a potential role for trait effects in delay discounting. Although previous smaller studies have shown impaired executive function, in our large sample size on chronic MMT we only observed impaired associative learning related to depressive and anxiety symptoms highlighting a role for managing comorbid symptoms to further optimize cognitive function.

**Keywords:** methadone; addiction; impulsivity; executive function; drug craving

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## 1. Introduction

Opioid use disorder is a major international public health issue with marked mortality, morbidity and high rates of relapse (Hser et al., 2017). Impulsivity is generally regarded as rapid, poorly considered premature actions without appropriate foresight and despite negative consequences (Dalley and Robbins, 2017). High impulsivity may further increase relapse rates of drug use (Adinoff et al., 2007). Greater impulsivity has been consistently shown across substance addictions such as methamphetamine, heroin and alcohol (Banca et al., 2016; Jones et al., 2016; Paydary et al., 2016).

Methadone maintenance treatment (MMT) has been proven safe and effective in decreasing opioid use or facilitating abstinence (Joseph et al., 2000). However, some studies report increased impulsivity in patients under methadone maintenance treatment, e.g. subjects with illicit opioid dependence who subsequently started on MMT show greater delay discounting than healthy controls (Robles et al., 2011; Scherbaum et al., 2018). Similarly, enhanced non-planning impulsivity has been reported (Baldacchino et al., 2015; Tolomeo et al., 2016). However, findings on impulsivity and MMT have been inconsistent, e.g. motoric impulsivity as measured by the Stop Signal task was found to be either worse or not significantly different in MMT when compared to healthy controls (Zeng et al., 2016; Liao et al., 2014) and risky behaviour assessed with the balloon analogue risk task was unaffected (Khodadadi et al., 2010). Notably, these studies were conducted with small sample sizes, ranging from over a dozen to around sixty participants, and lack systematic examination of multiple types of impulsivity whilst controlling for possible deficits in executive processing. Studies using larger sample sizes that examine potential covariates are needed to facilitate the interpretation of the research in this field (Baldacchino et al., 2017).

Here we focus on measures pertaining to different types of impulsivity and craving in MMT patients compared to healthy individuals on a larger cohort while controlling for executive functions, which might be different between the two groups (Wang et al., 2013). First, we systematically examined different types of impulsivity (delay discounting, reflection impulsivity, risk taking and motoric impulsivity), executive functions (spatial working memory, paired associative learning and strategic planning) and cue-induced craving in a large cohort of patients on MMT and compare them with healthy controls. Furthermore, we explored whether the abnormal impulsivity levels observed in the patients were related to psychological variables or MMT-related variables.

## 2. Materials and Methods

All procedures used in the present study were approved by the ethics committee of Ruijin Hospital, Shanghai Jiao Tong University School of Medicine. The reimbursement for time was ¥50 per hour. All participants gave their written informed consent following the Declaration of Helsinki.

### 2.1 Participants

The MMT outpatients were recruited from three MMT clinics in Xuhui, Hongkou and Yangpu districts, Shanghai. The age-matched (+/-5 years) healthy volunteers (HVs) were recruited via advertisement from Ruijin hospital and Hongkou MMT clinic, mainly consisted of caregivers, cleaners and security guards, as well as family members, relatives or friends of the outpatients or inpatients at Ruijin Hospital which focuses on neurological disorders. No family members of MMT outpatients were recruited. The control cohort was selected to have similar educational attainment to that of the MMT outpatients. The participants were recruited from June 2018 to January 2019. The demographic information of MMT outpatients was checked monthly using one-way ANOVA in SPSS to assess the recruitment demographic for HV recruitment and ensure matching of age, gender and educational level between the groups.

Participants were assessed by an addiction psychiatrist for mental health status and history using the Mini International Neuropsychiatric Interview (MINI Plus, version 5.0; Sheehan et al., 1998). The inclusion criteria of patients were: aged between 18 and 65; on daily MMT for at least one month and not using illegal drugs other than methadone (confirmed by monthly urine tests at the clinics). The exclusion criteria for both patients and HVs were: severe psychiatric disorders such as psychotic disorders or bipolar disorder, neurological illnesses, or head injury. Patients had a history of opioid dependence before starting on MMT. Previous use of other substances was allowed, assuming the history of opioid dependence was the primary substance use disorder and the other substances did not fit the criteria for substance use disorder. Patients last received MMT approximately 24 hours prior to the psychological and cognitive assessment.

### 2.2 Demographic and psychological questionnaires

The demographic information, current methadone dose and duration, and the history of drug use were collected. Participants' depression, anxiety, and impulsivity levels were respectively measured by the Beck Depression Inventory (BDI), State-Trait Anxiety Inventory (STAI) and UPPS-P Impulsive Behaviour Scale (measuring different aspects of impulsive personality: positive urgency, negative urgency, sensation seeking, lack of premeditation, and lack of perseverance). Smoking status was collected and nicotine dependence level related to cigarette smoking was measured by the Fagerstrom Test for Nicotine Dependence (FTND). Additionally, the withdrawal symptoms of the patients were graded via the Subjective Opiate Withdrawal Scale (SOWS).

**2.3 Study procedure and task description**

The MMT patients completed the questionnaires and the tasks in a quiet room at one of the three MMT clinics, and the HVs completed the questionnaires and the tasks at Ruijin Hospital or at the MMT clinic in Hongkou district.

Impulsivity was measured via: Delay Discounting Task (DDT), Beads Task, Balloon Analogue Risk Task (BART) and Stop Signal Task (SST). Executive functions tasks were: Spatial Working Memory (SWM), Paired Associative Learning (PAL) and Stockings of Cambridge (SOC). Craving levels induced by drug pictures were measured via a Drug Rating Task. The DDT, BART, Beads Task, and the Drug Rating Task were assessed on a 14-inch laptop (Lenovo Thinkpad X1) with a Windows 10 operating system. The SST, SWM, PAL and SOC were assessed on a 9.7-inch iPad (4th generation) using the Cambridge Neuropsychological Test Automated Battery (CANTAB) Connect Research iPad version (https://www.cambridgecognition.com/cantab). The participants either completed all of the tasks, which took about 70 minutes, or performed parts of the test battery due to being unavailable or unable to complete the study. The order of the tasks was randomized.

**2.3.1 DDT**

The DDT measures temporal discounting, which involves weighing future versus immediate outcomes. The DDT using small, medium and large delayed rewards (Kirby and Marakovic, 1996) was computerized using Psychtoolbox (Brainard, 1997). In each trial, the participants were asked to choose between an immediate and a delayed hypothetical monetary reward. Previously, no differences were found when comparing actual and hypothetical rewards (Madden et al., 2003). The side of presenting immediate vs. delayed rewards was counterbalanced across participants. The rate of discounting, $k$, *was* computed according to $k=(A/V-1)/D$, where $V$ is the present value of the delayed reward $A$ at delay $D$. A larger $k$ value indicates larger temporal discounting, and vice versa.

Due to the skewed nature of the *k* value, a natural logarithmic transformation was applied to the *k* value for statistical analysis. Participants with consistency ratings below 75% were excluded. The effects of small, medium, large delayed rewards (within-subject) and group (between-subject) were analysed.

**2.3.2 Beads Task**

The beads task, which measures reflection impulsivity, was programmed in E-Prime and published previously (Banca et al., 2016). Participants saw two jars with differing ratios of red and blue beads (Jar 1: $P_{red}$=0.80, $P_{blue}$=0.20; Jar 2: $P_{red}$=0.20, $P_{blue}$=0.80). The participants were instructed that beads would be individually picked by the computer from one of the two jars until they acquired a reasonable guess which jar the computer picked the beads from, and were informed that the maximum number of beads drawn equaled 20 per jar pair. Each drawn bead was continuously on the screen to reduce working memory load. After indicating their guess, the participants rated their level of confidence in their guess using a sliding bar (anchored at ‘not confident’ and ‘very confident’). Three trials without feedback were presented using a previously validated order of beads (Moutoussis et al., 2011). The fewer number of beads drawn before the guess being made indicates higher reflection impulsivity.

**2.3.3 BART**

The BART (Lejuez et al., 2002) measures risk-taking under ambiguity while balancing losses and rewards. The participants were asked to earn points by choosing between pumping the balloon up, which was rewarded with five points if the balloon did not burst, and banking the already earned points. They were told that more pumps might lead to a larger reward, but that the balloon can randomly burst after each pump, which results in all points for that trial being lost. The task used (Snowden et al., 2017) was programmed and presented using in-house software and consisted of 20 trials, with maximum pumps per balloon set to 16. The measures are the mean number of pumps and the proportion of banked trials. A larger number of pumps suggests a higher level of risk taking.

**2.3.4 SST**

The SST measures response inhibition, the ability to stop an ongoing action when interrupted by a cue. The participants responded to an arrow (go signal), which pointed either to the right or left by tapping the corresponding side of the iPad screen. The participants were instructed to inhibit their already initiated motor response when an auditory stop signal was presented. The stop-signal delay was modulated in steps of 50 ms based on participant's stop performance. We assessed stop-signal reaction time (SSRT), the slower the SSRT, the higher the motoric impulsivity (Logan et al., 1984).

### 2.3.5 SWM Task

The SWM task measures the capacity to retain and manipulate spatial information. On the screen, multiple boxes appear in an increasing order which when tapped revealed a token within. All tokens were to be dropped in a column and the participants were instructed to not return to the box where they previously found a token. The measure is the total number of errors (returning to the box where a token was previously found), which reflects spatial working memory (Owen et al., 1990).

### 2.3.6 PAL Task

The PAL task tests paired-associate memory and learning and requires the participants to recall a location previously paired to an object. On screen, a set of boxes automatically opened revealing an object/pattern one at a time in a randomized order. Later, each of these patterns was displayed one at a time in the centre of the screen, and participants were asked to identify the box previously associated to the pattern. We measured the total number of errors (reflecting paired-associate learning) and the number of patterns reached (Owen et al., 1995).

### 2.3.7 SOC Task

The SOC task evaluates spatial planning which requires individuals to use problem-solving strategies. The participants were shown two images stacked row-wise, where the top image had three stockings suspending three coloured balls. The participants were required to move the balls in the bottom image in order to copy the top pattern. The balls could be moved only one at a time and were accompanied by a maximum number of allowed moves. We measured the total number of moves to complete a 5-move problem and the total number of stages (reflecting strategic planning) completed.

### 2.3.8 Drug Rating Task

In this task, 90 individual stimuli showing either heroin images (from images obtained online in China), or neutral or negative pictures from the International Affective Picture System (IAPS; Lang et al., 1997) were presented in equal amounts using the software Presentation. Each picture was shown for 1.5 seconds and separated by a fixation cross (random duration between 1 to 3 seconds; in steps of 50 ms). After each set of 10 pictures of the same category, the participants were asked "How strongly do you want to use drugs/methadone/heroine right now?" and participants indicated their craving levels using a slider on the screen ranging from not at all (0 pixels) to very strongly (720 pixels). We analysed the effects of picture type (within-subject) and group (between-subject).

### 2.4 Statistics

Scores on the tasks greater than 3 standard deviations (*SD*s) from their group mean (*M*) were excluded as outliers. The number of participants who completed the tasks and the number of participants who were included for analyses (after exclusion of outliers) are listed in Table 1. All statistical analyses were carried out using SPSS version 25 (IBM Corp., Armonk, NY). A *Chi*-square test was used to test potential differences in categoric variables (e.g., gender, smoking status) between the two groups. Univariate ANOVAs were used for other between-group comparisons related to demographics, psychological measurements or task outcomes. Repeated-measure ANOVAs were used in the analyses with within-subject factors (DDT and Drug Rating Task). As the threshold of statistical significance, $p = 0.05$ was used.

## 3. Results

### 3.1 Demographics and psychological questionnaires

A hundred and fifteen MMT patients and 115 HVs were recruited in the study. The demographic information, current methadone dosage, and duration of MMT are listed in Table 2. There were no significant between-group differences in gender, age or education (*p*s > 0.08, Table 2). Among the participants, 111 MMT patients and 104 HVs completed BDI, STAI, and UPPS-P, and patients consistently scored higher than HVs (*ps* < 0.05, Table 3). A hundred and eleven MMT patients and 114 HVs reported their smoking status and cigarette smoking was significantly more common in MMT patients (107 out of 111, 96.4%) than in HVs (39 out of 114, 34.2%, $p < 0.001$). Similarly, nicotine dependence level, measured by FTND, was greater in the smoking MMT patients ($M = 4.74$, $SD = 2.64$) than in HVs ($M = 1.02$, $SD = 1.84$, $p < 0.001$). The mean SOWS scores of the patient group, indicating the withdrawal symptom at the moment of performing tasks, was 9.79 ($SD = 11.26$).

### 3.2 Cognitive measures

### 3.2.1 DDT

The repeated-measures ANOVA on the log transformed *k*-values (less negative ln transformed *k*-values reflect higher untransformed *k*-values) revealed a significant main effect of delayed reward magnitude ($p < 0.001$, Table 4) and a significant main effect of group ($p = 0.001$), but the interaction between group and reward magnitude was not significant ($p = 0.783$). The significant group difference was due to the patients having less negative ln(*k*) values (steeper delay discounting) than the HVs across reward magnitudes (Figure 1A).

### 3.2.2 Beads Task

The patients drew no fewer beads compared with the HVs ($p = 0.407$, Figure 1B, Table 4), but had significantly lower mean confidence ratings ($p = 0.049$).

### 3.2.3 BART

No statistically significant differences were revealed between groups for the mean pump score ($p = 0.182$, Figure 1C, Table 4), adjusted mean pumps ($p = 0.376$), or the mean proportion of banked trials ($p = 0.209$).

### 3.2.4 SST

The mean SSRT of the patients was significantly shorter than that of the HVs ($p = 0.003$, Figure 1D, Table 4).

### 3.2.5 SWM Task

There was no significant difference in the number of errors between patients and HVs ($p = 0.183$, Figure 1E, Table 4).

### 3.2.6 PAL Task

The patients made significantly more errors than the HVs ($p = 0.002$, Figure 1F, Table 4), while the number of reached patterns was also statistically different ($p = 0.007$).

### 3.2.7 SOC Task

The patients did not utilize significantly more moves than the HVs to successfully complete the 5-move problem ($p = 0.091$, Figure 1G, Table 4). The number of stages completed within the required number of moves was not statistically different between the groups ($p = 0.074$).

### 3.2.8 Drug Rating Task

The repeated-measures ANOVA on the craving ratings for neutral, negative and drug pictures revealed significant main effects of group ($p < 0.001$) and picture type ($p = 0.021$), as well as a significant interaction between group and type of picture ($p = 0.018$), as shown in Figure 1H and Table 4. Patients consistently rated themselves to experience significantly higher craving levels than HVs regardless which pictures were shown beforehand ($t$s > 12.749, $p$s < 0.001). The craving induced by drug pictures ($t(106) = 3.385$, $p = 0.001$), but not by negative pictures ($t(106) = 1.794$, $p = 0.076$), were significantly higher than those induced by neutral pictures in the patients, whilst in the HVs no such effect was observed (negative vs. neutral: $t(80) = 0.910$, $p = 0.365$; drug vs. neutral: $t(80)= 0.135$, $p = 0.893$).

### 3.3 Correlations between significant variables and psychological/addiction-related variables

As the patients scored significantly higher on depression and anxiety (Table 3), we also assessed the necessity of using these variables as covariates (Supplementary Table S1). The inclusion of the covariates, which showed significant correlations with task measures, did not alter the results of DDT, BART, SOC and Drug Rating tasks. The significant difference on confidence rating of the Beads task was no longer significant after the inclusion of BDI, STAI-S and STAI-T scores as covariates, and the significant difference on PAL task was no longer significant after the inclusion of BDI, STAI-S and STAI-T scores (Supplementary Table S2).

The performance on impulsivity and craving tasks were also covaried for the performance on executive functions tasks, either individually or in the form of a combination of variables which significantly correlated with the measures of impulsivity tasks (Supplementary Table S3). After introducing the covariates of executive functions, none of the between-group results changed (Supplementary Table S4).

Significant positive correlations were found between the delay-discounting rate in the large magnitude condition and the urgency scores on UPPS-P in the patients after regressing out the depression and anxiety scores (positive urgency: $r = 0.273$, $p = 0.005$; negative urgency: $r = 0.231$, $p = 0.018$; Figure 2A). There was also a significant positive correlation between the drug-picture-induced craving scores and the positive urgency scores in patients after regressing out the depression and anxiety scores ($r$ = 0.247, $p$ = 0.011; Figure 2B). No other task measures were significantly correlated with scores on UPPS-P.

The confidence rating of the Beads task also showed a negative correlation with the duration on MMT (Figure 2C, Supplementary Table S5). The performance on DDT, SST and PAL did not significantly correlate with any of the addiction-related variables (craving ratings, withdrawal symptoms, daily dosage of methadone and duration on MMT) or the FTND scores ($|rs| < 0.165$, $ps > 0.103$, Supplementary Table S5). The smoking and non-smoking HVs did not differ significantly in the majority of tasks ($ps > 0.152$), except for a significant interaction between DDT reward magnitude and smoking status ($p$ = 0.019, Supplementary Table S6). Most of the results comparing smoking patients to smoking HVs are in line with those reported previously including smoking and non-smoking participants. However, comparing smokers only, no significant between-group difference in the PAL task was observed (Supplementary Table S6).

The SOWS scores correlated significantly with the craving ratings when shown drug ($r$ = 0.280, $p$ = 0.004, Figure 3A) and negative ($r$ = 0.270, $p$ = 0.005, Figure 3B) pictures, but not with craving scores following neutral pictures ($r$ = 0.136, $p$ = 0.164, Figure 3C).

## 4. Discussion

We demonstrate that MMT patients have greater delay discounting and cue-induced craving relative to HVs. Although patients showed lower confidence ratings, this was accounted for by their depression and anxiety scores. On the other hand, no significant difference was observed in risk taking and better motoric response inhibition was found in MMT patients compared to controls. These impulsivity findings were not related to associative learning, craving measures, indices of methadone use severity or nicotine dependence. Impairments in associative learning observed in the patients were no longer significant when controlled for depression and anxiety symptoms suggesting an important role for comorbid symptoms in influencing cognitive function in MMT patients.

High impulsivity in substance use disorder has been observed in previous studies (Banca et al., 2016; Jones et al., 2016; Paydary et al., 2016) and heightened impulsivity may contribute to relapse (Adinoff et al., 2007). Methadone has been used as maintenance treatment for heroin addiction since the 1960s (Joseph et al., 2000) and the impulsivity profile in MMT patients has been reported with smaller sample sizes (Baldacchino et al., 2017; Baldacchino et al., 2015; Khodadadi et al., 2010; Liao et al., 2014; Robles et al., 2011; Scherbaum et al., 2018; Tolomeo et al., 2016; Zeng et al., 2016).

In the present study, we systematically examined multiple aspects of impulsivity in MMT patients. Our results indicate that, compared to HVs, MMT patients have increased temporal discounting, while risk taking is not statistically different. The higher reflection impulsivity in the patients were accounted for by depressive and anxiety symptoms. The patients showed significantly less motoric impulsivity than HVs, suggesting that MMT might potentially reduce the response inhibition deficits commonly observed in long-term drug abusers (Liao et al., 2014; Yang et al., 2015). Our larger sample size, testing of multiple impulsivity types and controlling for executive function in the same group of MMT patients, improves the reliability of our findings. Our patient sample has been maintained on methadone for more than seven years on average, which doubles the mean MMT duration of the previous studies (Baldacchino et al., 2017). Critically, the results suggest that under chronic MMT, the patients only have deficits in a specific form of impulsivity, namely the capacity to wait for delayed rewards.

Different aspects of impulsivity have distinct yet overlapping cortical and subcortical neural substrates (Dalley and Robbins, 2017; Voon and Dalley, 2016). ‘Stopping’ impulsivity is regulated by the dorsostriatal-dependent mechanisms (Duann et al., 2009) while premature responding implicates ventromesial prefrontal cortices and ventral striatum (Morris et al., 2016). Impulsive choice or temporal discounting has been considered to be associated with impaired function of the lateral prefrontal cortex (LPFC) and ventral striatum (Banca et al., 2016; Vanyukov et al., 2016). Our findings that MMT patients have elevated temporal discounting may suggest potential abnormalities in LPFC and ventral striatal regions. In line with this, MMT patients were recently shown to have decreased LPFC volumes (Lin et al., 2018) and BOLD response to a monetary incentive delay task (Yip et al., 2016). Opiate-dependent patients with MMT also showed diminished BOLD ventral striatal responses during reward and loss processing (Gradin et al., 2014).

Our findings highlight the role of an overall increase in drug craving. In particular, significant correlations were observed between the severity of withdrawal symptom and cue-induced, and negative-affect-induced cravings, suggesting cue-induced and negative-affect-induced cravings may be influenced by the state of withdrawal from methadone. Our findings support the role of cue-induced craving for incentive salience theories (Drummond, 2001).

Other cognitive functions including attention, memory, psychomotor speed, verbal function, decision making, and emotional interpretation have been shown to be affected in MMT patients (Baldacchino et al., 2017; Wang et al., 2013). Studies have revealed impairments in executive functions such as working memory (Baldacchino et al., 2019; Darke et al., 2000; Mazhari et al., 2015; Mintzer and Stitzer, 2002; Rapeli et al., 2007; Yin et al., 2012), paired associative learning (Baldacchino et al., 2019) and strategic planning (Baldacchino et al., 2015) in MMT patients. Here, although we noted an impairment on paired associative learning, this finding appeared to be driven by depression and anxiety. We show no statistical differences in working memory or strategic planning in MMT patients relative to HVs. This lack of difference may be related to our larger sample size and longer duration of MMT in the patients tested. Impairments in working memory, associative learning and strategic planning in previous studies may be related to chronic heroin exposure which with a sufficient duration of abstinence on MMT might normalize to a level similar to HVs. However, this requires a longitudinal study to confirm.

This study is not without limitations. Firstly, the acute effect of methadone on cognition was not examined in our present study, as the patients performed the tasks before taking their daily methadone, approximately 24 hours from the last methadone intake. Secondly, the lack of a clinical control group is a weakness of the study and future research might benefit from adding a comparison group consisting of individuals with opioid use disorder not receiving MMT to elucidate the specific influence of methadone on impulsivity and executive functions.

Put together, our findings in chronic MMT patients highlight an impairment in a specific form of decisional impulsivity, namely delay discounting with improved motor response inhibition functioning. That delay discounting remains impaired might suggest its role as a trait impairment that might precede and possibly predict opioid use disorder. We show a persistence of cue-induced craving symptoms correlating with withdrawal symptoms. Although various MMT studies have suggested impairments in executive function, notably our findings in a relatively large sample on chronic MMT do not confirm these observations and highlight a role for managing comorbid depressive and anxiety symptoms to further optimize cognitive functioning.

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**Contributors**

AM, KW, JD, CZ, BS, and VV were responsible for the study concept and design. JL, YZ, QR, ZZ, HZ, and HJ contributed to the acquisition of behavioural data. KW programmed Presentation and PsychToolbox paradigms. JL,YZ, and VV assisted with data analysis and interpretation of findings. JL, KW, AM and SW drafted the manuscript. QR, ZZ, HZ, HJ, JD, CZ, BS, and VV provided critical revision of the manuscript for important intellectual content. All authors critically reviewed content and approved final version for publication.

**Declaration of Competing Interest**

No conflict declared.

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## Figure Captions

**Figure 1.** Mean behavioural scores of the cognitive measures per MMT patients and HVs. **(A)** ln(*k*) scores across reward conditions on the Delay Discounting Task. **(B)** Number of beads drawn on the Beads Task. **(C)** Pump scores on the Balloon Analogue Risk Task. **(D)** Stop-signal reaction times on the Stop Signal Task. **(E)** Number of errors on the Spatial Working Memory Task. **(F)** Total number of errors on the Paired Associative Learning Task. **(G)** Total number of moves to complete a 5-move problem on the Stockings of Cambridge Task. **(H)** Self-reported craving scores following the presentation of drug, negative and neutral pictures. * indicates statistical significance ($p < 0.05$). Error bars indicate standard deviations. HVs = Healthy Volunteers.

**Figure 2.** Significant correlations between task measures and psychological/addiction-related variables in the patients. Pearson's correlation **(A)** between delay discounting and urgency, **(B)** between drug picture-induced craving and positive urgency, and **(C)** between confidence rating of Beads task and MMT duration. BDI = Beck Depression Inventory; DDT= Delay Discounting Task; MMT = methadone maintenance treatment; STAI-T = State-Trait Anxiety Inventory (trait version); STAI-S = State-Trait Anxiety Inventory (state version).

**Figure 3.** Patients' correlations between SOWS-based withdrawal state and cue-induced craving. Correlations between SOWS and **(A)** craving scores induced by drug pictures, **(B)** craving scores induced by negative pictures, **(C)** craving scores induced by neutral pictures. SOWS= Subjective Opiate Withdrawal Scale.

**Tables**

**Table 1.** The numbers of participants per task pre and post outlier removal

| Task Name | Number of Patients | | Number of HVs | |
|---|---|---|---|---|
| | Completed the Task | Included in Analyses | Completed the Task | Included in Analyses |
| DDT | 115 | 109 | 114 | 104 |
| Beads | 111 | 110 | 114 | 112 |
| BART | 105 | 105 | 95 | 95 |
| SST | 98 | 95 | 93 | 93 |
| SWM | 100 | 99 | 93 | 93 |
| PAL | 101 | 99 | 88 | 85 |
| SOC | 95 | 95 | 91 | 91 |
| Drug Rating | 107 | 107 | 89 | 81 |

*Note.* BART = Balloon Analogue Risk Task; DDT = Delay Discounting Task; HVs = Healthy Volunteers; PAL = Paired Associative Learning; SOC = Stockings of Cambridge; SST = Stop Signal Task; SWM = Spatial Working Memory.

**Table 2.** Demographic information, current methadone dosage and duration

| | Patients (n = 115) | | HVs (n = 115) | | Between-group Comparison | |
|---|---|---|---|---|---|---|
| | *M* (*SD*) | Range | *M* (*SD*) | Range | Statistics | *p* Value |
| Age (years) | 50.0 (8.2) | 32 to 64 | 48.2 (7.8) | 31 to 65 | $F(1,229)=2.927$ | 0.088 |
| Education (years) | 10.3 (1.9) | 6 to 16 | 10.1 (3.3) | 3 to 19 | $F(1,229)=0.252$ | 0.616 |
| Duration of MMT (months) | 89.6 (52.1) | 2 to 224 | | | | |
| Methadone Dosage (milligrams per day) | 44.9 (28.8) | 2 to 150 | | | | |
| Gender (male/female) | 83/32 | | 76/39 | | $\chi^2(1)=0.998$ | 0.318 |

*Note.* HVs = Healthy Volunteers; MMT = Methadone Maintenance Treatment; *M* = Mean; *SD* = Standard Deviation.

**Table 3.** Scores on BDI, STAI and UPPS-P in patients (n=111) and HVs (n=104)

| | BDI | STAI | | UPPS-P | | | | |
|---|---|---|---|---|---|---|---|---|
| | *M* (*SD*) | State | Trait | Positive Urgency | Negative Urgency | Sensation Seeking | Lack of Premeditation | Lack of Perseverance |
| Patients | 14.25 (10.96) | 36.65 (11.37) | 42.35 (11.01) | 30.92 (10.14) | 29.02 (7.63) | 28.00 (7.67) | 22.37 (5.57) | 20.54 (3.98) |
| HVs | 7.86 (7.67) | 30.34 (8.52) | 35.20 (8.54) | 24.12 (7.35) | 23.62 (7.14) | 24.66 (7.10) | 20.69 (4.70) | 18.12 (4.49) |
| Statistics *F*(1,214) | 24.258 | 20.994 | 28.037 | 31.375 | 28.633 | 10.909 | 5.655 | 17.607 |
| *p* Value | *p*<0.001 | *p*<0.001 | *p*<0.001 | *p*<0.001 | *p*<0.001 | *p*=0.001 | *p*=0.018 | *p*<0.001 |

*Note.* HVs = Healthy Volunteers; MMT = Methadone Maintenance Treatment; *M* = Mean; *SD* = Standard Deviation; BDI = Beck Depression Inventory; STAI = State-Trait Anxiety Inventory

**Table 4.** Group comparison results per task.

| **Paradigm** | **Task Variable** | **MMT Patients** *M* (*SD*) | **HVs** *M* (*SD*) | **Cohen's *d*** | | **Statistics** | ***p* value** |
|---|---|---|---|---|---|---|---|
| DDT | Small ln(k) | -3.62 (1.85) | -4.54 (1.97) | 0.48 | Group | ***F*(1,211)=12.258** | **0.001** |
| | Medium ln(k) | -4.18 (1.87) | -5.00 (1.95) | 0.43 | Magnitude | ***F*(1.915,404.161)=59.482** | **<0.001** |
| | Large ln(k) | -4.52 (1.94) | -5.37 (1.94) | 0.44 | Interaction | *F*(1.915,404.161)=0.233 | 0.783 |
| Beads | Mean Beads | 7.39 (5.22) | 7.95 (4.79) | 0.11 | | *F*(1,220)=0.690 | 0.407 |
| | Confidence | 458.34 (82.95) | 481.67 (92.27) | 0.27 | | ***F*(1,220)=3.918** | **0.049** |
| BART | Mean Pumps | 6.49 (1.16) | 6.72 (1.21) | 0.19 | | *F*(1,198)=1.790 | 0.182 |
| | Adjusted Pumps | 5.62 (1.09) | 5.76 (1.12) | 0.13 | | *F*(1,198)=0.788 | 0.376 |
| | Bank Proportion | 0.56 (0.15) | 0.53 (0.16) | 0.19 | | *F*(1,198)=1.587 | 0.209 |
| SST | SSRT | 265.78 (53.60) | 295.59 (79.02) | 0.44 | | ***F*(1,186)=9.198** | **0.003** |
| SWM | Total Errors | 16.85 (7.71) | 15.18 (9.52) | 0.19 | | *F*(1,190)=1.785 | 0.183 |
| PAL | Total Errors | 28.57 (14.11) | 22.45 (12.64) | 0.46 | | ***F*(1,182)=9.461** | **0.002** |
| | Patterns Reached | 7.29 (0.96) | 7.65 (0.77) | 0.41 | | ***F*(1,182)=7.460** | **0.007** |
| SOC | 5-move Problem | 8.37 (2.20) | 7.85 (1.98) | 0.25 | | *F*(1,184)=2.893 | 0.091 |
| | Stages Completed | 6.26 (2.57) | 6.85 (2.44) | 0.24 | | *F*(1,184)=3.222 | 0.074 |
| Drug | Neutral | 208.75 (153.34) | 7.91 (31.92) | 1.81 | Group | ***F*(1,186)=182.544** | **<0.001** |
| Rating | Negative | 233.26 (175.52) | 11.30 (35.03) | 1.75 | Type | ***F*(1.924,357.894)=3.991** | **0.021** |
| | Drug | 258.31 (186.70) | 7.42 (31.03) | 1.87 | Interaction | ***F*(1.924,357.894)=4.158** | **0.018** |

*Note.* Significant effects are highlighted in bold. Cohen's *d* indicates the effect size. HVs = Healthy Volunteers; MMT = Methadone Maintenance Treatment; *M* = Mean; *SD* = Standard Deviation; BART = Balloon Analogue Risk Task; DDT = Delay Discounting Task; PAL = Paired Associative Learning; SOC = Stockings of Cambridge; SST = Stop Signal Task; SSRT = Stop-Signal Reaction Time; SWM = Spatial Working Memory.

Figure 1 (revised)

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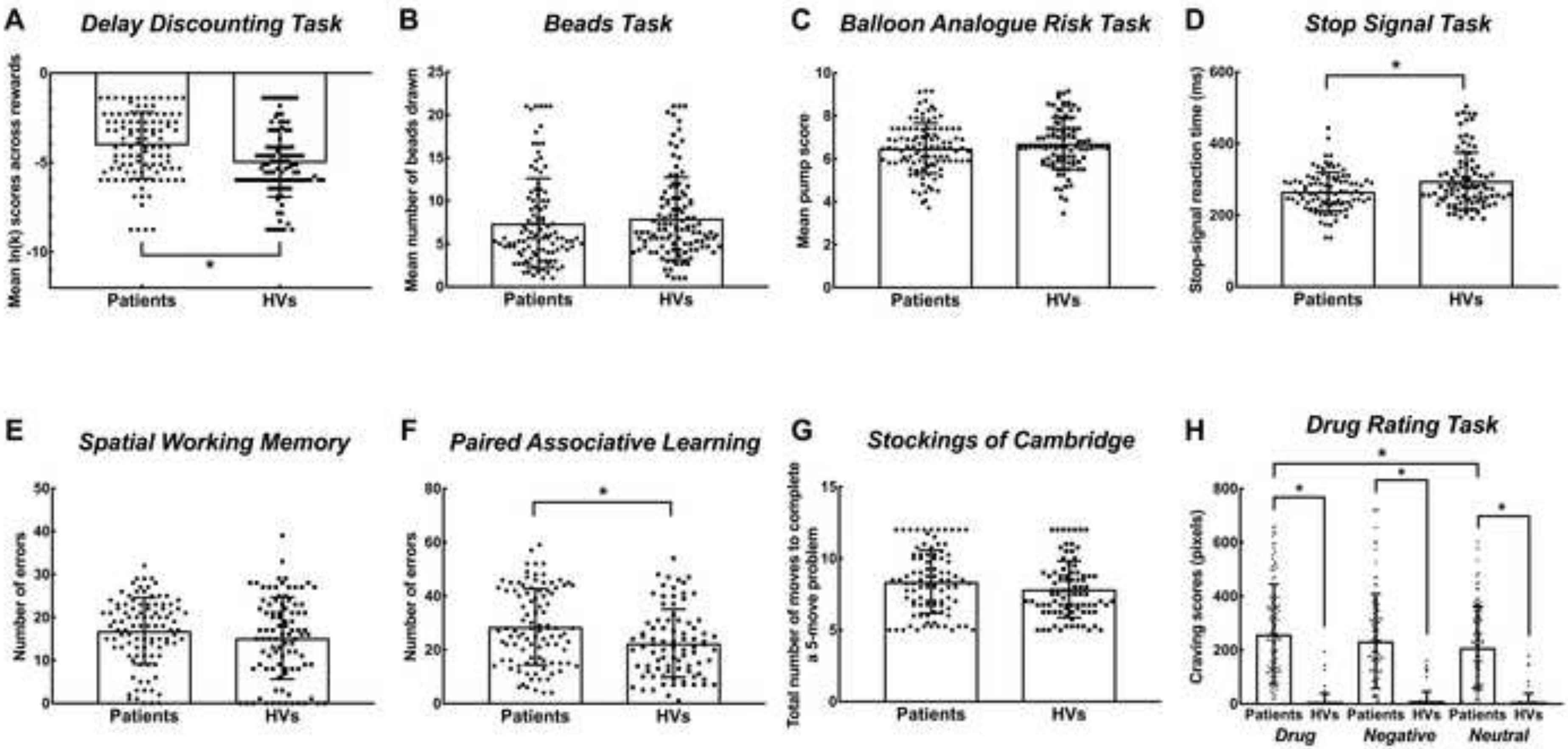

Figure 2 (revised)

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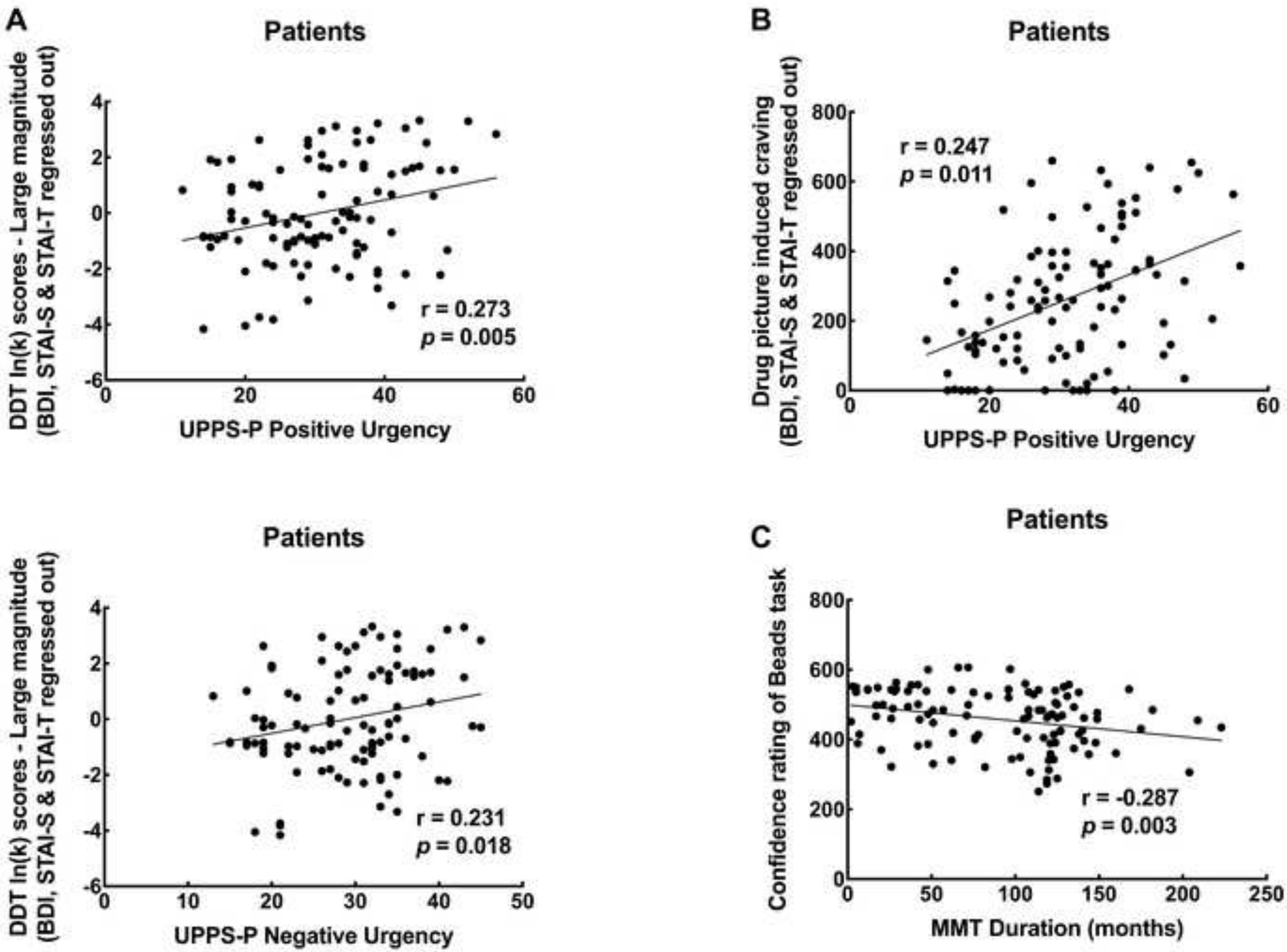

Figure 3

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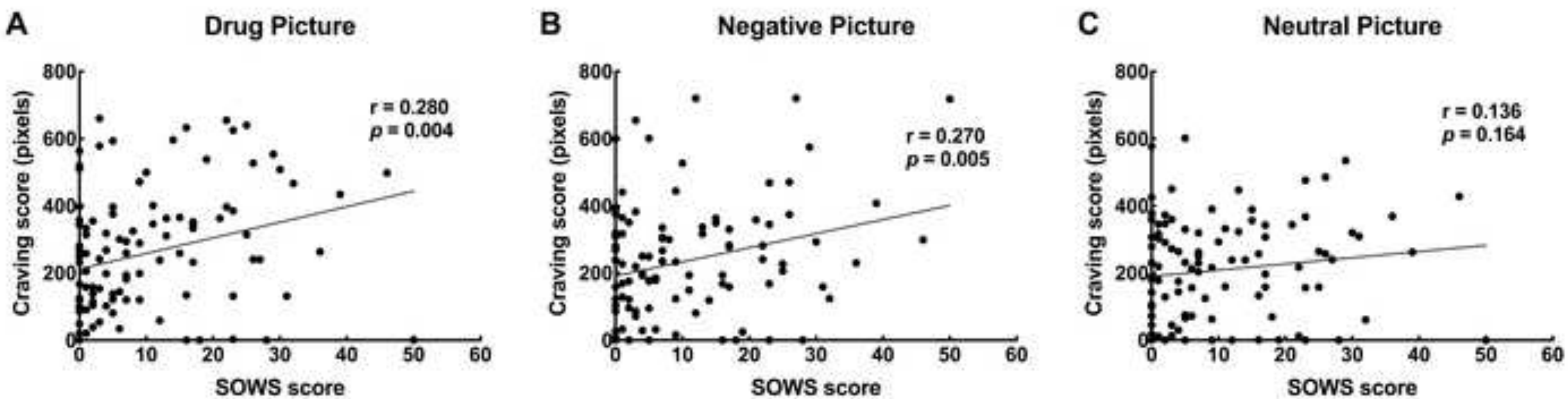

**Highlights**

- Cognitive functions under methadone maintenance treatment (MMT) were assessed.
- Delay discounting increases, but other forms of impulsivity are normal in patients.
- Impaired associative learning in MMT patients is related to depression and anxiety symptoms.
- Increased delay discounting and craving are correlated with impulsive personality scores.
- Cue-induced drug craving in MMT patients is modulated by withdrawal symptoms.