A randomized controlled trial of the effects of working memory training in methadone maintenance patients

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Abstract

Objective—Working memory impairment in individuals with chronic opioid dependence can play a major role in cognitive and treatment outcomes. Cognitive training targeting working memory shows promise for improved function in substance use disorders. To date, cognitive training has not been incorporated as an adjunctive treatment for opioid dependence.

Methods—Methadone maintenance patients were randomly assigned to experimental ($n = 28$) or active control ($n = 28$) 25-session computerized training and run in parallel. Cognitive and drug use outcomes were assessed before and after training.

Results—Participants in the experimental condition showed performance improvements on two of four working memory measures, and both groups improved on a third measure of working memory performance. Less frequent drug use was found in the experimental group than in the

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control group post-training. In contrast to previous findings with stimulant users, no significant effect of working memory training on delay discounting was found using either hypothetical or real rewards. There were no group differences on working memory outcome measures that were dissimilar from the training tasks, suggesting that another mechanism (e.g., increased distress tolerance) may have driven drug use results.

Conclusions—Working memory training improves performance on some measures of working memory in methadone maintenance patients, and may impact drug use outcomes. Working memory training shows promise in patients with substance use disorders; however, further research is needed to understand the mechanisms through which performance is improved and drug use outcomes are impacted.

Keywords

Methadone maintenance; Cognitive impairment; Memory training; Working memory; Delay discounting

1. Introduction

Opioid dependence is associated with impairment spanning multiple cognitive domains that may negatively affect daily psychosocial function, drug use behavior, and response to substance abuse treatment (Ersche and Sahakian, 2007; Gruber et al., 2007; Mintzer and Johnson, 2007; Rass et al., 2014). Deficits in working memory (WM) and in frontal brain regions thought to mediate WM have been observed in methadone maintenance patients, current opioid abusers not maintained on methadone, and abstinent opioid abusers (Darke et al., 2000; Ersche et al., 2006, 2005; Guerra et al., 1987; Lee et al., 2005; Mintzer and Stitzer, 2002; Ornstein et al., 2000; Papageorgiou et al., 2001; Pezawas et al., 2002; Piratsu et al., 2006; Prosser et al., 2006; Rapeli et al., 2007; Verdejo et al., 2005). WM, which is the ability to briefly hold on-line and manipulate small amounts of information to serve current goals, has important implications for daily functioning in healthy individuals and those with substance use disorders. WM is a core component of executive functions that select, initiate, monitor, and modulate other cognitive activities (Baddeley, 1992; Bechara and Martin, 2004; D'Esposito, 2007; Jurado and Rosselli, 2007; Repovs and Baddeley, 2006; Miyake et al., 2000). Substance abuse is associated with impaired performance on tasks involving working memory and executive function (e.g., inhibitory control, risk-taking, decision-making; Dretsch and Tipples, 2008; Finn et al., 1999; Hinson et al., 2003; Süß et al., 2002). Poor performance on WM and other tasks involving executive function predicts treatment outcomes in cognitively based substance use interventions, as reflected in higher dropout rates, less efficacious therapy, and greater susceptibility for relapse (Aharonovich et al., 2006, 2008; Dallery and Raiff, 2007; Grenard et al., 2008; Katz et al., 2005; Passetti et al., 2008; Schmitz et al., 2009; Teichner et al., 2001; Turner et al., 2009; Vocci, 2008).

Though few studies are available, recent work shows promise in using WM training to treat cognitive deficits that may limit the efficacy of behavioral and pharmacological interventions for substance use disorders (Houben et al., 2011; Bickel et al., 2011; Hinson et al., 2003; MacKillop et al., 2011; Shamosh et al., 2008). Significant and lasting improvement in WM following working memory training has been reported in several

populations with poor working memory skills, and transfer to some non-trained cognitive tasks has been observed (Klingberg et al., 2005; McNab et al., 2009; Olesen et al., 2004; Thorell et al., 2009; Westerberg and Klingberg, 2007; Westerberg et al., 2007). For example, Bickel et al. (2011) found that working memory training decreased delay discounting in stimulant users, suggesting greater preferences for larger-later rewards relative to smaller-sooner ones. In contrast, increased delay discounting is typically associated with poor working memory function and substance use disorders (e.g., Ahn et al., 2011; Hinson et al., 2003; Kirby and Petry, 2004; MacKillop et al., 2011). To date, there have been no studies of WM training in opioid users. We sought to address this gap and evaluate the effects of WM training on cognitive and drug use outcomes in methadone maintenance patients.

2. Methods

2.1. Participants

Individuals in methadone treatment for at least 2 months and on a stable methadone dose for at least 1 month were recruited from outpatient treatment programs in Baltimore, Maryland. Of 73 randomized participants, 56 completed the study (Fig. 1). Exclusion criteria were major untreated medical conditions (e.g., hypertension, diabetes), untreated Axis-I psychiatric disorders except substance abuse and dependence based on DSM-IV-TR criteria (Hudziak et al., 1993, 2004), use of any psychoactive drug other than caffeine and/or nicotine >4 times per week, daily alcohol consumption, or any condition associated with significant cognitive impairment (e.g., history of severe head trauma, HIV, ADHD). Participants without sufficient capacity to complete training and/or assessment (based on Shipley Institute of Living Scale estimated IQ and staff judgment) were also excluded (Zachary et al., 1985). Participants gave written informed consent and received compensation for participating. The Johns Hopkins University Institutional Review Board approved the study procedures.

2.2. Procedures

2.2.1. General procedures—Participants were randomly assigned to experimental or active control computerized training conditions using a minimization procedure (Pocock, 1983; Scott et al., 2002) to balance groups on age (18–34 and 35–55 years[1]), gender, estimated IQ (95 and >95), methadone treatment duration (2–6 months and >6 months), and methadone dose (90 mg and >90 mg). Participants completed 25 training sessions and pre- and post-training assessment sessions during trough methadone levels. Before every session, opioid withdrawal was assessed using a 20-item list of withdrawal-symptom adjectives (Strain et al., 2000). Acute alcohol intoxication was assessed using an Alco-Sensor IV (Intoximeters, Inc., St. Louis, MI) and behavioral tasks from the Brief Standardized Field Alcohol test (National Highway Traffic Safety Administration; Stuster and Burns, 1998). The session was rescheduled if the participant showed signs of opioid withdrawal, drug or alcohol intoxication, or fatigue, or had already taken his/her methadone before the session.

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[1]One participant was enrolled who exceeded the age limit due to staff error.

2.2.2. Training sessions—Training consisted of 25 45-min sessions 3–5 times per week at the study site. Research assistants monitored participants throughout each session. The training program (Cogmed QM; Cogmed Inc.) consisted of 12 exercises (8 per session) that require the maintenance and manipulation of sequences of verbal and/or visuo-spatial information in working memory (Klingberg et al., 2002, 2005). Three exercises were common across all sessions, whereas the other five varied. Training in the experimental condition involved an adaptive procedure in which difficulty (i.e., number of stimuli, or level) increased as proficiency was achieved, whereas training in the control condition consisted of a static procedure wherein the number of stimuli was always two. Experimental participants also received performance feedback. For the experimental condition, performance on training sessions was indexed using measures of improvement for the three training exercises completed at every session. Learning was calculated using a longitudinal linear model fit of the highest level obtained at each session, with session number as the covariate, and adjusted for highest level attained at baseline for each exercise. The performance variable *learning slope* was calculated as the average of the learning slopes for these three exercises that were completed at every session.

2.2.3. Pre- and post-training assessment sessions—Participants completed pre- and post-training assessment sessions that were administered by a research assistant blind to training condition (with one exception due to error). To avoid interference with methadone dosing schedules, both assessment sessions were split into two 1.5-h sessions over two separate days.

2.3. Cognitive outcomes

A detailed description of cognitive outcome measures can be found in Supplementary Materials.

2.3.1. Working memory—Working memory was assessed using verbal and nonverbal measures. Dependent measures included the following: (a) *Digit Span* (Wechsler, 1981): span length, forward and backward; (b) *Operation Span* (Turner and Engle, 1989; Engle et al., 1992): proportion of correctly recalled words; (c) *N-back Task* (Jonides et al., 1997; Mintzer and Griffiths, 2007): proportion of yes responses made to target letters (hit rate), proportion of yes responses made to non-target letters (false alarm rate), and signal detection measures of sensitivity in distinguishing between target and non-target letters (d') and response bias (C) (Snodgrass and Corwin, 1988); and (d) *Visuo-spatial Working Memory Task* (Rapport et al., 2008): proportion of correctly replicated sequences.

2.3.2. Episodic memory and metamemory—Episodic memory was assessed using *word recall* and *recognition*. Dependent variables were the proportion of old responses made to old words (hit rate), proportion of old responses made to new words (false alarm rate), sensitivity in distinguishing between old and new words (d'), and response bias (C) (Snodgrass and Corwin, 1988). *Metamemory* was evaluated by calculating the Goodman–Kruskal gamma correlation between confidence ratings and recognition memory accuracy, collapsed across old and new words for sufficient power (Goodman and Kruskal, 1954).

2.3.3. Psychomotor speed and attention, trail making test A and B—Halstead
(1947) and Reitan (1955) measured psychomotor speed and conceptual flexibility.
Dependent measures were completion time (in seconds), number of errors, and the
difference in time to complete B and A. *Digit Symbol Substitution Task* (DSST; McLeod et
al., 1982; based on Wechsler, 1981) measured focused attention. Dependent measures were
the number of trials attempted and the proportion of correct trials.

2.3.4. Reasoning, Raven's standard progressive matrices—Raven (1939)
assessed reasoning ability through the completion of patterns. The dependent measure was
the proportion of correct trials.

2.3.5. Response inhibition and self-control, a continuous performance task—
Epstein et al. (1998) measured response inhibition. Dependent measures were proportion of
correct non-X trials (hit rate), proportion of incorrect X-trials (false alarm), sensitivity in
distinguishing between non-X letters and X (d'), and response bias (C).

Two versions of the *Delay Discounting Task* measured self-control: (a) *Hypothetical Delay
Discounting Task* (Baker et al., 2003; Johnson and Bickel, 2002; Johnson et al., 2007, 2010),
and (b) *Quick Discounting Operant Task* (QDOT; Johnson, 2012), including actual
contingencies in terms of reward delivery and the requirement to wait to receive rewards
during the task.

A modified computerized version (Mintzer and Stitzer, 2002) of the *Iowa Gambling Task*
(Bechara et al., 1994) measured risk-taking and self-control. The dependent measure was
difference in number of cards selected from the advantageous versus disadvantageous decks,
calculated separately for the decks associated with high frequency (i.e., C minus A) and low
frequency (i.e., D minus B) of penalties, and collapsed across frequency of penalties [i.e. (C
plus D) minus (A plus B)].

2.3.6. Substance use and functional outcomes—Self-reported drug use history and
severity were assessed at baseline via a *Drug History Questionnaire. Timeline Follow Back*
assessed number of days of recent use of cocaine, opiates, benzodiazepines, cannabis, and
alcohol at pre- and post-assessment (Sobell and Sobell, 1996). Functional outcomes (i.e.,
composite measures for medical, employment, alcohol and other drug use, legal, family, and
psychiatric status) were assessed via the *Addiction Severity Index* (ASI; McLellan et al.,
1992) at pre- and post-assessment. Drug use during the study was assessed via urine
specimens tested for cocaine, opiates, benzodiazepines, and cannabis and via breathalyzer
for alcohol on training and assessment session days.

2.4. Statistical analyses

Data were analyzed with IBM SPSS Statistics version 20 (IBM Corporation, Armonk, NY),
GraphPad Prism version 5 (GraphPad Software, Inc., La Jolla, CA), and Stata version 13
(StataCorp, L.P., College Station TX). Participant characteristics were analyzed using *t-tests*
(age, years of education, estimated IQ, methadone treatment duration, and methadone dose)
and *chi-square analysis* (gender, race). For assessment outcomes, a two (group:
experimental vs. control) × two (session: pre- vs. post-training) mixed analysis of variance

(ANOVA) was used to assess main effects and interactions for all variables except n-back, visuo-spatial working memory, and delay discounting. The n-back task was analyzed using a two (group: experimental vs. control) × two (session: pre- vs. post-training) mixed effects model with a random intercept and 0-back condition as covariate. The visuo-spatial working memory task was analyzed using a two (group: experimental vs. control) × two (session: pre-vs. post-training) × three (condition: 3, 5, or 7 dots, or items) mixed effects model with a random intercept. Fisher's least significant difference (LSD) test was used to resolve significant interactions for post hoc analysis. All alpha levels were set at 0.05, and a Bonferroni correction for the working memory outcome measures set post hoc significance levels at $p < .005$.

For each of the two delay discounting tasks, delay discounting was quantified as the area under the curve metric (AUC; Myerson et al., 2001); AUC values can range from 0 to 1, with greater values indicating less delay discounting, or greater preference for later-later rewards. We assessed the orderliness of the discounting data by applying criterion 1 described by Johnson and Bickel (2008). Self-reported drug use history was analyzed using *chi-square* analysis for past month, year, and lifetime use for each drug. Heroin and cocaine use severity was analyzed using *t-tests*. Delay discounting AUC, Timeline follow back, and ASI composite measures were analyzed using a two (group: experimental vs. control) × two (session: pre- vs. post-training) mixed analysis of variance (ANOVA) for each functional outcome. Changes in odds of positive urine over time were compared between groups using a longitudinal logistic regression model that controlled for baseline urine status. The logistic regression model included baseline value, session, condition, and session × condition interaction, and the correlation matrix was exchangeable. Correlations between repeated urines within participants were handled using the method of generalized estimating equations (GEE; Zeger and Liang, 1986).

3. Results

3.1. Participant characteristics (Table 1)

There were no significant group differences in age, gender, race, estimated IQ, years of education, days in methadone treatment, or methadone dose (Table 1). The experimental groups did not significantly differ on the number of days to complete the training (control group $M = 44.3$ [$SD = 8.9$] days; experimental group $M = 45.2$ [$SD = 10.4$] days; $t[2,54] = -0.36$; $p = 0.72$). For baseline measures of drug use, more participants in the experimental group reported using nicotine in the past year ($X^2[1] = 8.114$, $p = .004$) and in their lifetime ($X^2[1] = 7.791$, $p = .005$) (Table 2) compared to control group participants. Additionally, participants in the experimental group reported spending significantly more money per week on heroin than participants in the control group prior to study entry ($t[54] = -2.207$, $p = .032$).

3.2. Cognitive performance (Tables 3 and 4)

3.2.1. Working memory—For the digit span task, a group × session interaction ($F[1,54] = 8.176$, $p = .006$) and main effect of session ($F[1,54] = 9.659$, $p = .003$) showed that experimental participants improved significantly on digit span backward following training

compared to control participants. The interaction was driven by a significant improvement over time for the experimental group (*LSD p* < .001). There was no significant effect on digit span forward. For the operation span task, a main effect of session (*F*[1,54] = 7.672, *p* = .008) showed that both groups recalled a significantly higher proportion of words at the post-training assessment. For the visuo-spatial working memory task, a group × session interaction (*β* = 0.116, SE = 0.051, *p* = .023) showed improved performance on the visuo-spatial working memory task for the experimental group, but not for the control group (Fig. 2). There was a significant effect of condition (*p* < .001) and a non-significant attenuation of the improvement as task difficulty (i.e., number of items) increased. There were no significant effects on n-back task performance.

3.2.2. Episodic memory and metamemory—A main effect of group (*F*[1,53] = 4.143, *p* = .047) showed that the experimental group recalled more words overall. For the recognition memory task, main effects of session showed an increase in false alarm rate (*F*[1,53] = 13.427, *p* = .001), and decreases in *d′* (*F*[1,53] = 6.024, *p* = .017) and *C* (*F*[1,53] = 8.428, *p* = .005) in the post-training session relative to pre-training in both conditions. There were no significant effects on metamemory.

3.2.3. Psychomotor speed and attention—A main effect of session (*F*[1,54] = 5.620, *p* = .021) showed that both groups completed Trail Making Test A faster at the post-training assessment relative to pre-training. Digit Symbol Substitution task performance showed a trend for more trials attempted at the post-training assessment (*F*[1,53] = 3.757, *p* = .058).

3.2.4. Reasoning—A main effect of session (*F*[1,54] = 7.696, *p* = .008) showed worse performance on Raven's Matrices for both groups at the post-training assessment.

3.2.5. Response inhibition and self-control—For the continuous performance task, main effects of session showed decreased response time variability (*F*[1,54] = 7.391, *p* = .009), a decrease in hits (*F*[1,54] = 7.001, *p* = .011), and a decrease in *d′* (*F*[1,54] = 4.361, *p* = .042) in the post-training session relative to pre-training in both conditions.

For the QDOT data, 3 and 1 participants, in the control and experimental groups, respectively, failed the orderliness criterion in either of the two assessments. For the hypothetical delay discount task data, 4 and 2 participants, in the control and experimental groups, respectively, failed the orderliness criterion in either of the two assessments. Eliminating these participants case-wise within each analysis did not affect whether any result met significance. Therefore, results are reported for the full data set. For the QDOT, which delivered real rewards, there was a significant main effect showing decreased discounting at post-training compared to pre-training (*F*(1,53) = 5.291, *p* = .03), however neither the main effect for group of the group × session interaction was significant. For the hypothetical discounting task, neither main effect nor their interaction was significant.

There were no significant effects on Iowa Gambling Task performance.

3.3. Substance use and functional outcomes

The timeline follow back measure of drug use showed a significant session × condition interaction for any substance use frequency across both 14-day ($F[1,54] = 4.275$, $p = .043$) and 30-day ($F[1,54] = 5.726$, $p = .020$) time periods (Table 5). Post hoc analysis showed that participants in the control condition reported significantly more drug use days at the post-training assessment compared to pre-training (14 day assessment, 2.93 vs. 1.29 days, *LSD p* = .002; 30 day assessment, 6.04 vs. 2.39 days, *LSD p* < .001), but no significant effect was found for experimental group participants. Participants in the experimental group reported fewer drug use days at the post-training assessment compared to control participants (14 day assessment, 1.32 vs. 2.93 days, *LSD p* = .045; 30 day assessment, 2.64 vs. 6.04 days, *LSD p* = .048). Addiction Severity Index composite scores revealed a significant main effect of session ($F[1,53] = 4.111$, $p = .048$) indicating improved employment status at the post-training assessment for both conditions, but no other significant differences.

To increase power, analysis of positive urine screens was collapsed across drugs [i.e., cocaine, opiates, benzodiazepines, and cannabis (THC)] (Fig. 3). At baseline, participants in the experimental group were less likely to have positive urines (OR = 0.65, 95% CI = 0.25, 1.65), but the difference was not statistically significant. Among participants in the control group, the likelihood of a positive urine increased over time (OR = 1.01, 95% CI = 1.00, 1.02, $p = 0.040$), which can be interpreted as a 1% increase in odds of a positive urine with each session. There was no difference in slopes over time between the two groups (ratio of odds ratios = 1.00, 95% CI = 0.99, 1.01). These results were similar for each drug individually with the exception of THC. For THC, participants in the experimental group were more likely to have positive urines (OR = 2.35, 95% CI = 0.34, 16.28) at baseline, but the difference was not statistically significant. Among participants in the control group, the likelihood of a THC-positive urine increased over time (OR = 1.03, 95% CI = 1.00, 1.05, $p = 0.030$), which can be interpreted as a 3% increase in odds of a positive urine with each session. While rates of THC-positive urines were increasing over time in the control group, they were decreasing in the experimental group (ratio of odds ratios = 0.95, 95% CI = 0.92, 0.98, $p = 0.002$).

3.4. Training data

Analysis of experimental group training performance (based on the three training exercises that were done at every session) showed a positive learning slope ($M = 0.04$, $SD = 0.02$), consistent with an overall average training improvement of one item in working memory across 25 training sessions.

4. Discussion

The aim of the present study was to evaluate the efficacy of a working memory training program to improve cognitive and substance use outcomes in methadone maintenance patients. Following training, participants in the experimental group showed improvement on working memory measures (Digit Span and Visuospatial Working Memory). Moreover, biological measures indicated that control participants' drug use increased during the study, whereas experimental participants' use remained constant. These results are promising and

similar to past findings with working memory training in problem drinkers, who showed improved performance on working memory tasks and reduced drinking (Houben et al., 2011).

Despite improvement on working memory measures similar to training tasks, there was no improvement on dissimilar measures of working memory. Specifically, working memory improvements in the experimental group were limited to tasks similar to those participants were trained on (i.e., visuospatial working memory, digit span backward). Improvement on operation span, an un-trained working memory measure, was found for both groups and was therefore attributed to practice effects. These findings are consistent with Bickel et al. (2011), who did not find improvements in working memory following working memory training in stimulant users, Houben et al. (2011), whose outcome measures of WM performance consisted of the tasks participants had trained on, and other working memory training studies that found no generalization to working memory measures dissimilar from the training tasks (i.e., no "near transfer" occurred; see Shipstead et al., 2012 for review). Furthermore, no improvement was found in other cognitive domains (i.e., no "far transfer" occurred), similar to results reported by Bickel et al. (2011) with the exception of the null results for delay discounting. Whether this reflects a difference between stimulant and opioid users is unknown and may be addressed by future research. Thus, these findings contribute to the controversy regarding WM training effectiveness and generalization (e.g., Morrison and Chein, 2011; Klingberg, 2012; Melby-Lervag and Hulme, 2013; Shipstead et al., 2012).

Delay discounting was not differentially affected by working memory training as hypothesized. Our confidence in these results, however, is bolstered by the use of both a widely used hypothetical task as well as a task that delivers real rewards in real time, and by the fact that the discounting results were largely orderly (i.e., consistent with the expectation of stable or monastically decreasing values with increasing delays). Although our study did not show significant differences between groups, both groups showed significantly decreased discounting as measured by the real-rewards QDOT task, and both groups showed non-significant decreases in delay discounting in the hypothetical task, potentially consistent with the notion that working memory training and the control task challenged distress tolerance. Persistence in an energy-depleting task that may be challenging (e.g., adaptive training) or boring (e.g., control training) may evoke uncomfortable emotional states (e.g., negative affect, frustration, craving). In addition, both conditions required participants to sit quietly and focus for prolonged periods of time, an experience that they may not typically encounter in their daily lives. Evidence suggests that delay discounting is increased under conditions in which one is restricted from other sources of reward during delays (Johnson et al., 2015). As implied by the expression "a watched pot never boils," such waiting conditions may be described as "frustrating," and decisions for delayed outcomes may therefore be affected by distress tolerance. The ability to cope with feelings of frustration that may arise as task difficulty increases is important in working memory training, as is maintaining focus for prolonged periods. Thus, augmenting working memory training with training of coping skills, emotional regulation, or mindfulness may enhance both cognitive performance and psychosocial treatment outcomes (Bowen et al., 2009; Brewer et al., 2009; Desbordes et al., 2012; Garland et al., 2010; Sahdra et al., 2011; Witkiewitz et al., 2013).

This tactic may be especially relevant for individuals with substance use disorders, who often exhibit deficits in emotion regulation (Gerra et al., 2003; Witkiewitz et al., 2012; Wong et al., 2013).

These findings suggest that cognitive training is feasible and potentially beneficial for individuals with opioid use disorders. Participants were able to learn and showed improvement on some working memory and drug use outcomes. However, further research is needed to determine the contribution of individual differences (e.g., cognitive abilities, psychiatric comorbidities, motivational/personality factors, distress intolerance) and the role of training regimen (e.g., modality, frequency, intensity, duration, feedback) on training efficacy and to assess the persistence of improved outcomes (Dunning and Holmes, 2014; Jaeggi et al., 2014; von Bastian and Oberauer, 2013).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.drugalcdep.2015.08.012.
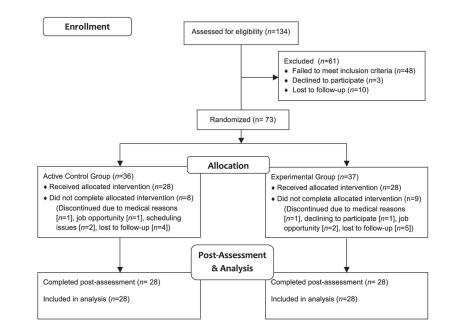
Fig. 1.
CONSORT flow diagram. Experimental group participants who did not complete the study attended an average of 9.3 sessions ($SD = 6.1$, range = 3–19). Control group participants who did not complete the study attended an average of 9.1 sessions ($SD = 5.5$, range = 0–15).
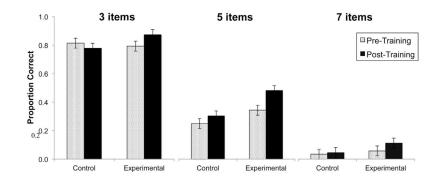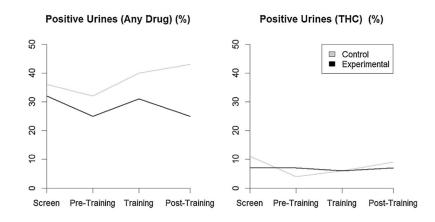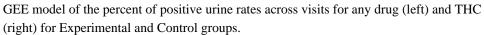
Fig. 2.
Visuo-spatial working memory performance as a function of group for pre-training assessment and post-training assessment. Data represent fitted (model-based) means ±1 standard error of the mean. Analysis showed a group × session interaction and a main effect of condition ($ps < .05$).

Fig. 3.
GEE model of the percent of positive urine rates across visits for any drug (left) and THC (right) for Experimental and Control groups.

Table 1

Participant characteristics.

Variable	Control ($n = 28$)		Experimental ($n = 28$)	
	M	*SD*	*M*	*SD*
Age in years	43.5	7.1	43.3	8.8
Years of education	11.1	1.9	11.8	1.9
Shipley IQ	88.4	11.7	88.3	11.8
Months in methadone treatment	2.9	0.4	2.9	0.4
Methadone dose (mg)	99.3	25.3	96.5	19.0
	%	*n*	%	*N*
Race				
Black	79	22	68	19
White	18	5	32	9
Sex				
Female	57	16	50	14
Male	43	12	50	14

Note: X^2 and *t*-test analyses showed no significant group differences for these variables (all *p*s > 0.05). Although no group differences were found for methadone dose or duration in treatment, methadone dose is not well-correlated with methadone blood levels (Eap et al., 2000).

Table 2

(A) Self-reported prevalence of drug use. (B) Self-reported severity of drug use.

A

Drug	Control (n = 28)			Experimental (n = 28)		
	Lifetime	Past year	Past month	Lifetime	Past year	Past month
Heroin	100 (28)	25 (7)	11 (3)	100 (28)	50 (14)	4 (1)
Alcohol	96(27)	61 (17)	36 (10)	96 (27)	54 (15)	43 (12)
Cocaine	93 (26)	43 (12)	21 (6)	89 (25)	46 (13)	21 (6)
Caffeine	86 (24)	86 (24)	86 (24)	93 (26)	89 (25)	89 (25)
Nicotine	68 (19)	61 (17)	61 (17)	96 (27)	93 (26)	82 (23)
Cannabis	79 (22)	21 (6)	18 (5)	89 (25)	25 (7)	18 (5)
Benzodiazepine	32 (9)	18 (5)	11 (3)	46 (13)	14 (4)	4 (1)
Hallucinogen	7 (2)	0	0	11 (3)	0	0
Amphetamine	0	0	0	0	0	0

B

Drug	Control			Experimental		
	Years used	$ per day	$ per week	Years used	$ per day	$ per week
Heroin	18.3 (8.1)	67 (78)	419 (487)	18.6 (10.0)	108 (82)	738 (590)
Cocaine	17.4 (10.3)	43 (62)	216 (442)	16.6 (11.1)	52 (83)	316 (603)

Note: Values represent % (*n*) of participants reporting use. Data are missing for amphetamine use at all times for one control participant and for past month heroin use for one experimental participant. Groups did not differ on reported drug use history with the exception of nicotine in the past year ($X^2[1] = 8.114$, $p = .004$) and lifetime ($X^2[1] = 7.791$, $p = .005$).

Values represent *Mean* (*Standard Deviation*). Data are missing from two control and three experimental participants regarding cocaine spending. Groups did not differ on years of drug use or money spent on cocaine. The experimental group reported spending significantly more money per week on heroin than the control group ($t[54] = -2.207$, $p = .032$).

Table 3

Performance on working memory and episodic memory tasks at pre-training and post-training assessment.

Measure	Control		Experimental	
	Pre-training	**Post-training**	**Pre-training**	**Post-training**
Digit span length				
Forward span	6.14 (1.18)	6.36 (1.22)	6.04 (1.11)	6.25 (1.18)
Backward span[b,c]	4.04 (1.04)	4.07 (1.09)	3.82 (0.98)	4.68 (1.34)
Operation span				
Proportion correct[b]	0.67 (0.15)	0.72 (0.12)	0.70 (0.13)	0.72 (0.13)
N-back (2-back)				
Hit rate	0.62 (0.21)	0.63 (0.18)	0.68 (0.19)	0.68 (0.22)
False alarm rate	0.21 (0.13)	0.19 (0.14)	0.17 (0.12)	0.16 (0.13)
d' (sensitivity)	1.33 (0.93)	1.36 (0.73)	1.61 (0.92)	1.69 (1.04)
C (response bias)	0.26 (0.43)	0.33 (0.38)	0.23 (0.32)	0.27 (0.37)
Visuo-spatial working memory[c]				
Proportion correct (3 items)	0.81 (0.14)	0.79 (0.16)	0.78 (0.22)	0.87 (0.12)
Proportion correct (5 items)	0.25 (0.22)	0.34 (0.26)	0.30 (0.27)	0.48 (0.29)
Proportion correct (7 items)	0.03 (0.07)	0.06 (0.10)	0.05 (0.12)	0.11 (0.17)
Free recall				
Mean # correct responses[a]	4.46 (3.24)	5.21 (3.51)	6.93 (4.61)	6.96 (5.12)
Recognition memory				
Hit rate	0.75 (0.12)	0.75 (0.13)	0.76 (0.14)	0.79 (0.13)
False alarm rate[b]	0.24 (0.14)	0.32 (0.21)	0.19 (0.14)	0.29 (0.19)
d' (sensitivity)[b]	1.50 (0.47)	1.35 (0.70)	1.75 (0.53)	1.54 (0.66)
C (response bias)[b]	0.02 (0.35)	−0.08 (0.47)	0.11 (0.44)	−0.09 (0.45)
Metamemory				
Gamma	0.31 (0.29)	0.15 (0.39)	0.35 (0.25)	0.32 (0.34)

Note: Values represent *Mean* (*Standard Deviation*). Superscript letters indicate significant main effect of group (a), main effect of session (b), or group × session interaction (c). Free recall and recognition memory data were missing from one of 28 participants in the experimental group. Metamemory data were missing from three of 28 participants in the control group and six of 28 participants in the experimental group.

Table 4

Performance on measures of psychomotor speed, attention, reasoning, response inhibition, and self-control at pre-training and post-training assessment.

Measure	Control		Experimental	
	Pre-training	Post-training	Pre-training	Post-training
Trail making test				
Trails A time (s)[b]	44.43 (19.21)	38.64 (13.23)	38.96 (14.23)	35.61 (12.11)
Trails B time (s)	124.25 (69.56)	113.46 (59.83)	108.36 (59.42)	107.46 (62.51)
Trails B-A time (s)	79.82 (66.74)	74.82 (54.48)	69.39 (56.30)	71.86 (58.92)
Trails B # errors	0.75 (1.27)	1.14 (1.43)	0.71 (1.36)	0.43 (0.92)
Digit symbol substitution test				
Number attempted[b]	18.25 (8.70)	20.75 (8.82)	21.52 (9.66)	21.59 (10.42)
Proportion correct	0.89 (0.21)	0.94 (0.09)	0.91 (0.13)	0.92 (0.15)
Raven's matrices				
Proportion correct (all sets)[b]	0.62 (0.15)	0.60 (0.16)	0.68 (0.14)	0.63 (0.15)
Continuous performance task				
Mean RT (s)	0.45 (0.11)	0.45 (0.09)	0.44 (0.08)	0.43 (0.07)
Standard error (s)[b]	0.01 (0.00)	0.01 (0.01)	0.01 (0.00)	0.01 (0.01)
Hit rate[b]	0.98 (0.03)	0.97 (0.04)	0.98 (0.03)	0.96 (0.06)
False alarm rate	0.22 (0.16)	0.23 (0.17)	0.22 (0.16)	0.25 (0.16)
d' (sensitivity)[b]	3.09 (0.82)	3.02 (1.05)	3.22 (0.93)	2.83 (1.11)
C (response bias)	−0.69 (0.30)	−0.65 (0.28)	−0.73 (0.27)	−0.64 (0.30)
Delay discounting				
Hypothetical AUC	0.22 (0.25)	0.21 (0.25)	0.29 (0.32)	0.27 (0.30)
QDOT AUC	0.60 (0.26)	0.66 (0.29)	0.63 (0.28)	0.74 (0.28)
Iowa gambling task				
Net difference	3.07 (28.16)	3.86 (27.66)	−0.23 (14.58)	1.46 (22.02)
Deck C-A	5.14 (14.52)	6.68 (15.13)	1.31 (9.85)	4.38 (12.43)
Deck D-B	−2.07 (15.96)	−2.82 (16.71)	−1.54 (10.75)	−2.92 (13.89)

Note: Values represent *Mean* (*Standard Deviation*). Superscript letters indicate significant main effect of group (a), main effect of session (b), or group × session interaction (c). Delay discounting data for the QDOT and Digit Symbol Substitution Task data were missing from one of the 28 participants in the experimental group. Iowa Gambling Task data were missing from two of 28 participants in the experimental group.

Table 5

Self-reported substance use and functional outcomes.

Measure	Control		Experimental	
	Pre-training	**Post-training**	**Pre-training**	**Post-training**
Timeline follow back (days used)				
Any substance: 14 days[b,c]	1.29 (2.12)	2.93 (3.54)	1.18 (1.79)	1.32 (2.16)
Any substance: 30 days[b,c]	2.39 (3.86)	6.04 (7.54)	2.32 (3.53)	2.64 (4.68)
Addiction Severity Index composite measures				
Alcohol	0.05 (0.09)	0.07 (0.16)	0.03 (0.06)	0.03 (0.07)
Other drugs	0.15 (0.08)	0.15 (0.11)	0.13 (0.07)	0.12 (0.06)
Employment status[b]	0.87 (0.16)	0.81 (0.23)	0.87 (0.17)	0.84 (0.20)
Family status	0.08 (0.14)	0.10 (0.20)	0.04 (0.13)	0.03 (0.08)
Legal status	0.05 (0.11)	0.07 (0.15)	0.03 (0.08)	0.03 (0.11)
Medical status	0.24 (0.30)	0.29 (0.37)	0.22 (0.31)	0.34 (0.33)
Psychiatric status[b]	0.06 (0.12)	0.12 (0.19)	0.02 (0.07)	0.05 (0.12)

Note: Values represent *Mean* (*Standard Deviation*). Superscript letters indicate significant main effect of group (a), main effect of session (b), or group × session interaction (c). Addiction Severity Index data were missing from one of the 28 participants in the experimental group.