Cognitive rehabilitation for individuals with opioid use disorder: A randomized controlled trial

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Cognitive rehabilitation for individuals with opioid use disorder: A randomized controlled trial*

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Abstract

Aim: To examine the efficacy of cognitive rehabilitation treatment (CRT) for people with opioid use disorder who were recruited into a methadone maintenance treatment (MMT) programme.

Method: 120 male subjects were randomly assigned to (1) MMT plus CRT in two months or (2) MMT plus a control intervention. Subjects were assessed at the beginning, mid-point and post-intervention as well as at 1-, 3- and 6-month follow-up time points.

Results: Analysis with repeated measure ANOVA showed that the CRT group performed significantly better in tests of learning, switching, processing speed, working memory and memory span. Moreover, the CRT group had significantly lower opiate use over the control group during 3-months follow-up. Analysis including only those with a history of methamphetamine use showed that the CRT group had significantly lower amphetamine use. No group differences were observed for treatment retention.

Conclusions: Our findings provide evidence that adding CRT as an adjunct intervention to MMT can improve cognitive performance as well as abstinence from both opiates and stimulants.

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Introduction

The prevalence of non-medical use of opioids, including heroin, has increased globally in past decades and represented a significant public health problem. The United Nations Office on Drugs and Crime (UNODC) reported that, in 2014, 33 million people worldwide use opioids (including opium and heroin)(UNODC, 2014).

Chronic use of opioids may lead to neurocognitive impairments associated with structural and functional abnormalities in the brain (Upadhyay et al., 2010). These neurocognitive impairments may be characterised by deficits in decision making, flexibility, impulsive control, reasoning, visuospatial skills, psychomotor speed, attention, concentration, verbal fluency and episodic memory among users (Brand, Roth-Bauer, Driessen, & Markowitsch, 2008; Gruber, Silveri, & Yurgelun-Todd, 2007; Guerra, Solé, Camí, & Tobeña, 1987; Prosser et al., 2006).

The neurocognitive impairments in substance use disorders (SUDs) interfere with daily life activities and treatment outcomes. People with SUDs who also have deficits in learning, memory, attention and executive functions have difficulty in managing finances or holding down their job, and also experience problems in everyday tasks including driving, interacting with family, regular attendance of treatment sessions and compliance with their medications (Cadet & Bisagno, 2016). Furthermore, neurocognitive impairments may contribute to poor treatment outcomes for SUDs, including high drop-out rates (Aharonovich, Nunes, & Hasin, 2003), low attendance at therapy sessions (Guthrie & Elliott, 1980), low willingness to change (Blume & Marlatt, 2009), reduced insight (Horner, Harvey, & Denier, 1999), denial of substance use problems (Rinn, Desai, Rosenblatt, & Gastfriend, 2002), impulsivity and higher rates of lapse and relapse to substance use following treatment termination (Aharonovich et al., 2006). These individuals may also have difficulty in processing the information that is conveyed in the course of treatment, and employing them in the context of their everyday lives (Rezapour, DeVito, Sofuoglu, & Ekhtiari, 2016).

Due to established associations between neurocognitive deficits and treatment outcomes in SUDs (Dean et al., 2009), optimal levels of neurocognitive functioning are proposed to be critical for successful treatment outcomes (Sofuoglu, DeVito, Waters, & Carroll, 2016; Sofuoglu, Sugarman, & Carroll, 2010). Therefore, targeting cognitive deficits could increase the overall efficacy of treatments for SUDs. Cognitive rehabilitation treatment (CRT) aims to improve cognitive functions including attention, memory and decision-making (Rezapour et al., 2016; Sofuoglu, DeVito, Waters, & Carroll, 2013). CRT consists of a set of techniques and strategies applied in a regular and repeated basis for those with brain-related injuries or disorders (Rezapour et al., 2015; Sofuoglu et al., 2013). Historically, CRT is mainly applied to patients with traumatic brain injury and stroke. Due to the promising results achieved in these disorders, CRT has also been adapted as an adjunct treatment in other neuropsychiatric disorders including schizophrenia, depression, anxiety and, more recently, SUDs (Bahar-Fuchs, Clare, & Woods, 2013).

Although evidence from a limited number of studies in SUDs shows promising results for the potential benefits of CRT as an adjunct treatment for the improvement of
cognitive functions and treatment outcomes (Alfonso, Caracuel, Delgado-Pastor, & Verdejo-García, 2011; Bickel, Yi, Landes, Hill, & Baxter, 2011), many critical questions remain to be addressed in well-controlled studies. First, given that most studies were conducted in individuals with alcohol use disorder (Godfrey & Knight, 1985; Houben, Wiers, & Jansen, 2011; Rupp, Kemmler, Kurz, Hinterhuber, & Fleischhacker, 2012), it is unclear if similar benefits from CRT may also be observed with other drugs of abuse, such as opioids. Second, it is unclear if the gains in cognitive function that are achieved during treatment are durable, because many studies have included assessment just after the treatment completion or a short (e.g., 1-month) time period after the treatment was completed (Houben et al., 2011). Lastly, the benefit of CRT as an adjunct to pharmacological interventions including methadone maintenance treatment (MMT) needs to be clarified, as there is plausible evidence that this type of intervention by itself may negatively affect cognitive functions among people who are receiving it (Prosser et al., 2006).

The primary goal of this study was to conduct a randomised clinical trial testing the efficacy of CRT as an add-on treatment to MMT in subjects with opioid use disorder. The outcome measures included both cognitive functioning and clinical outcomes over 6-month follow-up. We hypothesised that subjects who receive MMT plus CRT will show greater improvement in cognitive function and better SUD treatment outcomes than those who received MMT plus control intervention.

Methods

Participants

This was a randomised, single blind, parallel-group controlled trial. 120 subjects who fulfilled the DSM-V (The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) criteria for opioid use disorder were recruited from a court-mandated MMT residential centre between May 2015 and October 2016 in Iran. Subjects were supposed to remain in the centre for at least 2 months. Randomisation was performed by the last number of subjects’ ID cards (even = CRT, odd = control). Randomisation was performed by the centre receptionist, who was blinded to the type of intervention for each group.

Similar to other court-mandated centres, subjects were provided with daily methadone prescription and counselling sessions. Methadone was started at 30–40 mg/day and individually titrated as needed, following the MMT guidelines in Iran. After the stabilisation phase (at the end of the second week after admission), subjects received a stable dosage of methadone, ranging from 60 to 70 mg/day, for 2 months, until the time of discharge from the centre. After discharge, during the follow-up period, subjects received stable doses of methadone, ranging from 90 to 100 mg/day, in an outpatient certified MMT programme (National protocol published by Iran Ministry of Health for maintenance treatment of opioid users). Methadone treatment used in this study was according to MMT guidelines in Iran for residential MMT centres. Based on these guidelines, after discharging from a residential centre, physicians were allowed to increase the daily dose during the first 10 days (3 mg per day) as patients had reached a stabilised condition. During the follow-up period, subjects only received their daily methadone as medication and were provided with basic psychosocial interventions in outpatient methadone clinics.
Subjects were included in this study if they were 20–40 years of age, fulfilled DSM-V criteria for opioid use disorder and were able to speak and write Farsi sufficiently. Subjects were excluded from study participation if they had other major psychiatric (e.g., schizophrenia, bipolar disorder or major depression) or neurological disorders, had severe opioid withdrawal symptoms (as defined by Objective Opioid Withdrawal Scale > 6) at the end of the second week after admission (before entering the trial) or reported a recent history of suicide attempts. Written informed consent was obtained from all subjects after they were given a detailed explanation of the purpose and procedures of the study. It was also explained that their participation was entirely voluntary and, that they were free to withdraw at any time and that their refusal to continue would not jeopardise their treatment or legal rights. The residential and outpatient treatments were free of charge.

The study was approved by the independent ethics committee of the University of Social Welfare and Rehabilitation Sciences (USWR), Iranian Ministry of Health.

**Intervention**

Subjects randomised to the CRT group received CRT plus usual clinical care, which included MMT and counselling. CRT was conducted in a group setting, 1-hour session two times per week over 8 weeks. CRT was applied with the use of a recently developed NEuroCOgnitiveREhabilitation for Disease of Addiction programme (NECOREDA). NECOREDA is a paper-and-pencil training of cognitive functions that are commonly affected by SUDs: attention, memory, calculation, visuospatial process, verbal skills and reasoning (Rezapour et al., 2015).

In each session of training, 2–3 cognitive domains are targeted with gradually increasing difficulty over time (see Figure 1). In the final two sessions, training targets

![Figure 1. Architecture of NEuroCOgnitiveREhabilitation for Disease of Addiction programme (NECOREDA) exercises for 16 sessions.](image)

Note: Numbers indicate the level of difficulty of exercises for that session (1 = the easiest level to 5 = the most complex level).
all six cognitive domains with the highest level of difficulty. In addition to cognitive training, NECOREDA focuses on psychoeducational aspects of cognitive rehabilitation, including: metacognitive education, compensatory and lifestyle training. Subjects were encouraged to do homework between treatment sessions. Homework exercises were similar to those used in the treatment sessions. The NECOREDA is described in more detail, including examples of exercises and psychoeducation strategies, elsewhere (Rezapour et al., 2015).

Subjects in the control group received 16 1-hour group sessions plus the usual clinical care for 2 months. Painting in a group setting was chosen as a control intervention to minimise the plausible confounding effects of social interaction of the CRT, which was given in group settings. Painting has been used in previous studies as an active control intervention (Haimov, Shatil, & Laks, 2013; Trapp et al., 2013).

Assessments

Assessments of neurocognitive functions were administered at 6 time points: pre intervention (week 0 or T0), mid-point (week 4 or T1), post-intervention (week 8 or T2), 1-month follow-up (week 12 or T3), 3-month follow-up (week 20 or T4) and 6-month follow-up (week 32 or T5). The assessment team was blind to intervention allocation.

Neurocognitive assessments

Measures of cognitive functioning were selected based on their frequent use in previous studies of people with SUDs, including the following.

- Trial Making Test (TMT). The TMT measures psychomotor speed and attention consisting of two parts: TMT-A and TMT-B. In TMT-A, subjects are asked to connect numbers (1–23) by making lines. In contrast, in TMT-B, numbers and letters are randomly arranged on a page and subjects are asked to connect them in alternating order. The scores used are time needed to complete each part separately as well as time differences between TMT-A and TMT-B (Day, Celio, Lisman, Johansen, & Spear, 2013).
- Digit Span Test (DST). The DST assesses working memory and consists of two components: Forward Digit Span (FDS) and Backward Digit Span (BDS). In the FDS task, the subject hears a list of digits and is asked to simply repeat the sequence aloud. In the BDS, the subject is asked to repeat the sequence in reverse order. The scores used for FDS and BDS are the maximum number of series repeated correctly by participants (McAvinue et al., 2013).
- Stroop Colour-Word Test. The Stroop test, a frequently used test of executive functions, assesses the ability to withhold pre-potent responses. We used Dodrill’s version of the Stroop test, which is a classic paper-and-pencil version of the Stroop test. In this test, subjects are presented a list of 176 colour words in red, yellow, blue and green, which are printed in a non-matching colour. In the first part of the test, subjects read the printed words, while in the second part they are asked to name the colours those words are printed in. The number of errors and the time it takes to complete the second part, as well as time and error differences between the two parts (i.e., interference score), are used as measured variables (Buha & Gligorovic, 2016).
- Verbal Fluency Test (VFT). VFT is a test to assess verbal fluency, including phonemic (three letters) and semantic (two categories) fluency. Subjects are given 60 seconds
to generate aloud a list of words for each condition. The scores used were the average number of generated words in each phonemic and semantic separately (Suzuki et al., 2012).

- Ray Auditory Verbal Learning Test (RAVLT). RAVLT is a test to assess immediate and delayed memory and comprises an oral presentation of 15 words for 5 consecutive trials with immediate recall after each trial (Trials 1–5). Following an interference list, free recall trials occur at short and long delays (after 25 minutes). Finally, a yes/no recognition task is administered (Bleecker, 2005; Rezvanfard et al., 2011). Scores used in RAVLT were “total learning”, “learning over time”, “free delayed recall” and “word span”.

- Digit Symbol Substitution Test. This is a test to measure psychomotor performance, in which the subject is given a key grid of numbers and matching symbols and a test section with numbers and empty boxes. The test consists of filling as many empty boxes as possible with a symbol matching each number within 90 seconds. The score is the number of correct number–symbol matches (Rosano, Newman, Katz, Hirsch, & Kuller, 2008).

**Clinical assessments**

After admission, subjects were interviewed and responded to the Beck Depression Inventory (BDI) (Ghassemzadeh, Mojtabai, Karamghadiri, & Ebrahimkhani, 2005). A structured interview was used by a trained clinical psychologist for demographic factors and substance use details. The BDI was used to control the confounding effect of depression on the results of intervention. The Objective Opiate Withdrawal Scale was used to monitor the intensity of withdrawal symptoms at the first and second week of admission by an expert physician (Tompkins et al., 2009); it contains 13 physically observable signs, rated present or absent, based on a timed period of observation of the patient by a drug counsellor. Drug use and treatment retention were considered as secondary outcomes. Drug use was defined as amphetamine- and morphine-positive urine test results collected once a week and treatment retention was defined as regular attendance in the clinic to take daily and home doses of methadone (twice a week) during the follow-up period.

**Statistical analysis**

With a sample size of 120 and an expected attrition from assessments of 45%, the study had a power of 85% and a level of significance of 5% to detect a moderate effect \((d = 0.6)\). Descriptive statistics were used to characterise the population and the two groups were compared on baseline characteristics with a t-test. The assumption of normality of the distribution of all parameters was tested with Kolmogorov–Smirnov. For all parameters, the significance level was < 0.05, indicating a normal distribution. To facilitate data reduction, we used principal components analysis (PCA) after standardising all scores to identify main components. Based on loading factors, a composite score was formed for each identified component. For all extracted components, repeated-measures analysis of variance (ANOVA) was used. 6 time points were treated as the within-subjects factor (effect over time) and the differences in cognitive functions between the CRT and control groups were treated as the between-subjects factor. Analysis was performed with subjects who completed all assessments, and those
with missing values at one or more assessment time-point were excluded from analyses. Multiple comparison p-value thresholds were corrected with false discovery rate (Hochberg & Benjaminit, 1995). Post-hoc tests with least significant difference (LSD) correction were performed to compare within-group changes. For treatment outcomes, a t-test was used to compare the mean differences of measures at 1-, 3- and 6-month follow-up time points. To estimate the effect size of intervention, we used eta squared ($\eta^2$) for cognitive functions and Cohen’s d for treatment outcomes. All statistical analysis was performed using SPSS v.23.0. Due to the low rate of retention at 6-month follow-up (CRT group = 10, control group = 13), our emphasis was on 3-month follow-up results and data from 6-month follow-up interpreted cautiously. Data for this study is pre-registered and accessible on Open Science Framework (OSF), titled “Cognitive Rehabilitation for Individuals with Opioid Use Disorder”.

Results

Baseline characteristics

Subject flow is presented in Figure 2. A total of 120 subjects were recruited and allocated to either CRT or control groups using a 1:1 ratio. As shown in Tables 1 and 2, there was no significant difference between the two groups in terms of demographic and substance use characteristics or cognitive functions measured at baseline, except in FDS score.

Results from PCA

PCA was conducted on 16 neurocognitive measures assessed at 5 different time points (Supplementary Table 1). The varimax rotation was employed to ensure that each measure was maximally correlated with one principal component and had minimal associations with the other components. Before performing PCA, standard Z-scores were calculated separately for each measure. Based on eigenvalue decomposition of the 16 original measures, 6 significant principal components (with an eigenvalue >1) were extracted. These components explained 70.48% of the variance in the data and were identified as learning, working memory, switching, executive control, processing speed and memory span (Table 3). We performed PCA with data from 3-month follow-up (CRT group = 23, control group = 28) and used the extracted components for analysing data from 6-month follow-up.

Primary outcomes in 3-month follow-up

Table 4 presents a summary of mean scores corresponding to pre-, mid- and post-intervention as well as 1- and 3-month follow-up measurements. Repeated ANOVA was carried out and the main effects of time, intervention as well as time x intervention can be found in Table 4. Our findings indicated that there was a significant main effect of CRT on learning ($F(1,49) = 9.77, p = .01$, mean difference = 1.24, %95CI = [0.44,2.04]), switching ($F(1,49) = 6.38, p = .01$, mean difference = 0.71, %95CI = [0.14,1.28]), processing speed ($F(1,49) = 5.96, p = .01$, mean difference = 0.66, %95CI = [0.11,1.21]), working memory ($F(1,49) = 21.46, p = .01$, mean difference = 1.83, %95CI = [1.03,2.63]) and memory span ($F(1,49) = 5.61, p = .02$, mean difference = 0.18, %95CI = [0.02,0.34]).
measure the effect size, we used partial eta squared values ($\eta^2_p$) and interpreted the values according to Cohen (0.01 = small, 0.09 = medium and 0.25 = large) (Enz & Frosch, 2015). Analysis revealed the largest effect size in working memory ($h^2_p = 0.30$) and medium to large in learning ($\eta^2_p = 0.16$), switching ($\eta^2_p = 0.11$) and similarly in processing speed and memory span ($\eta^2_p = 0.10$). For learning-related tasks, we found a significant effect of the time and intervention interaction. Post-hoc analysis showed that the interaction effect was due to a significant improvement of performance in the CRT group between pre-intervention and 1-month follow-up (mean difference = $-0.67$, $p = .02$) and a significant deterioration of performance in the control group between pre-intervention and 3-month follow-up (mean difference = 0.82, $p = .01$). For switching-related tasks, we found a significant effect of the time and intervention interaction.

Figure 2. CONSORT diagram of flow of participants through the randomised controlled trial.
Post-hoc analysis also showed that the interaction effect was due to a significant improvement of performance between pre- and post-intervention (mean difference = −1.6, p = .01) in the CRT group and between mid-term assessment and post-intervention in the control group (mean difference = −1.17, p = .01), which remained stable over 3-month follow-up. A significant effect of the time and intervention interaction was also revealed in the case of processing speed for the CRT group between pre-intervention and 1-month follow-up (mean difference = −0.94, p = .01) and for the control group between pre- and post-intervention (mean difference = −0.49, p = .02), which remained stable over the next 2 months. For working-memory-related tasks, interaction effects were found in both groups, as the CRT group indicated improvement from admission to post-intervention (mean difference = −1.86, p = .000), which remained stable over the follow-up period, while, in the control group, working memory decreased from pre- to
post-intervention (mean difference = 0.87, \( p = .019 \)) and remained unchanged over the follow-up period. For the memory span component, we found a significant effect of the time and intervention interaction. Post-hoc analysis showed that the interaction effect was due to a significant improvement of performance between pre-intervention and 1-month follow-up in the CRT group (mean difference = −0.29, \( p = .04 \)) and a significant deterioration of performance between mid-term and 1-month follow-up in the control group (mean difference = 0.17, \( p = .03 \)), which remained stable during 3-month follow-up. The time effect on executive-control-related tasks in the control group was due to a significant improvement of performance of subjects between post-intervention and 3-month follow-up (mean difference = −0.52, \( p = .22 \)) (Figure 3).

**Secondary outcomes in 3-month follow-up**

Retention rate for both CRT (\( n = 23 \)) and control groups (\( n = 28 \)) from admission to 3-month follow-up were equally high and were not significantly different (39% in CRT and 47% in control, \( p = .51 \)). Although, it should be noted that the high rate of retention over the 2-month intervention (2 subjects from each group) indicates the feasibility of the CRT intervention in court-based residential MMT centres.

During 3-month follow-up, participants were required to attend biweekly visits, 24 visits in total, to receive methadone and their take-home doses. No significant group differences were observed for the mean number of missed visits (CRT group = 3.74 ± 4.74, control group = 3.57 ± 4.74 sessions) \( (T = 0.19, p = .84) \). In addition, in opiate-positive urines, out of 12 samples collected over 3 months (weekly), the rate was lower in the CRT group (2.35 ± 2.70) compared to the control group (3.51 ± 3.09) \( (T = −2.01, p = .04, \text{Table 3.} \)  

<table>
<thead>
<tr>
<th>Learning</th>
<th>Switching</th>
<th>Working memory</th>
<th>Processing speed</th>
<th>Executive control</th>
<th>Memory span</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVLT total learning</td>
<td>0.84</td>
<td>0.01</td>
<td>0.19</td>
<td>−0.08</td>
<td>0.01</td>
</tr>
<tr>
<td>AVLT learning over time</td>
<td>0.70</td>
<td>−0.01</td>
<td>0.05</td>
<td>−0.06</td>
<td>−0.04</td>
</tr>
<tr>
<td>AVLT delayed recall</td>
<td>0.84</td>
<td>−1.01</td>
<td>0.10</td>
<td>−0.15</td>
<td>−0.02</td>
</tr>
<tr>
<td>Stroop word-colour error</td>
<td>0.01</td>
<td>0.04</td>
<td>−0.09</td>
<td>0.14</td>
<td>0.93</td>
</tr>
<tr>
<td>Stroop word-colour error inference</td>
<td>−0.02</td>
<td>0.01</td>
<td>−0.08</td>
<td>0.11</td>
<td>0.94</td>
</tr>
<tr>
<td>Stroop word-colour time</td>
<td>−0.14</td>
<td>0.10</td>
<td>−0.06</td>
<td>0.69</td>
<td>0.20</td>
</tr>
<tr>
<td>Stroop word-colour time inference</td>
<td>−0.03</td>
<td>0.06</td>
<td>0.04</td>
<td>0.73</td>
<td>0.09</td>
</tr>
<tr>
<td>Trial making (A)</td>
<td>−0.04</td>
<td>0.22</td>
<td>−0.33</td>
<td>0.61</td>
<td>0.01</td>
</tr>
<tr>
<td>Forward digit span</td>
<td>0.24</td>
<td>−0.01</td>
<td>0.73</td>
<td>0.08</td>
<td>−0.11</td>
</tr>
<tr>
<td>Backward digit span</td>
<td>0.14</td>
<td>−0.05</td>
<td>0.76</td>
<td>−0.17</td>
<td>−0.12</td>
</tr>
<tr>
<td>Digit symbol substitution</td>
<td>0.22</td>
<td>−0.19</td>
<td>0.55</td>
<td>−0.47</td>
<td>0.01</td>
</tr>
<tr>
<td>Verbal fluency (letter)</td>
<td>−0.05</td>
<td>−0.12</td>
<td>0.40</td>
<td>−0.04</td>
<td>−0.01</td>
</tr>
<tr>
<td>Verbal fluency (category)</td>
<td>0.33</td>
<td>−0.01</td>
<td>0.35</td>
<td>−0.33</td>
<td>0.21</td>
</tr>
<tr>
<td>Trial making (B)</td>
<td>−0.05</td>
<td>0.93</td>
<td>−0.20</td>
<td>0.26</td>
<td>0.03</td>
</tr>
<tr>
<td>Trial making difference</td>
<td>−0.04</td>
<td>0.97</td>
<td>−0.11</td>
<td>0.08</td>
<td>0.03</td>
</tr>
<tr>
<td>AVLT word span</td>
<td>0.22</td>
<td>−0.04</td>
<td>−0.01</td>
<td>0.03</td>
<td>−0.03</td>
</tr>
</tbody>
</table>

Note: Rey indicates the variables included within a particular factor, determined based on the strongest factor loading for that variable.
### Table 4. Summary of pre-, mid-, post-intervention and 1- and 3-month follow-up measures and significant interactions on repeated ANOVA.

<table>
<thead>
<tr>
<th>Components</th>
<th>CRT group (n = 23)</th>
<th>Control group (n = 28)</th>
<th>Intervention F (p)</th>
<th>Time F (p)</th>
<th>Intervention × Time F (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T0</td>
<td>T1</td>
<td>T2</td>
<td>T3</td>
<td>T4</td>
</tr>
<tr>
<td>Learning</td>
<td>0.02 (1.79)</td>
<td>0.20 (1.74)</td>
<td>0.84 (2.29)</td>
<td>0.70 (1.83)</td>
<td>0.85 (1.87)</td>
</tr>
<tr>
<td>Switching</td>
<td>-0.52 (2.14)</td>
<td>-0.03 (1.34)</td>
<td>1.08 (0.86)</td>
<td>0.78 (0.70)</td>
<td>1.31 (0.52)</td>
</tr>
<tr>
<td>Processing speed</td>
<td>0.09 (0.75)</td>
<td>0.02 (2.28)</td>
<td>0.57 (2.49)</td>
<td>1.04 (0.77)</td>
<td>1.00 (0.89)</td>
</tr>
<tr>
<td>Working memory</td>
<td>-0.33 (1.19)</td>
<td>1.05 (1.64)</td>
<td>1.51 (1.70)</td>
<td>1.34 (1.58)</td>
<td>1.13 (1.76)</td>
</tr>
<tr>
<td>Executive control</td>
<td>-0.29 (2.22)</td>
<td>0.54 (0.50)</td>
<td>0.26 (1.06)</td>
<td>0.42 (0.89)</td>
<td>0.63 (0.55)</td>
</tr>
<tr>
<td>Memory span</td>
<td>-0.21 (0.61)</td>
<td>0.14 (0.39)</td>
<td>-0.01 (0.30)</td>
<td>0.08 (0.31)</td>
<td>0.15 (0.57)</td>
</tr>
</tbody>
</table>

Note: Values represent mean scores (SD between brackets).
No significant differences between groups were observed in F-test for variables (ns).
T0 = pre-intervention (week 0); T1 = mid-term (week 4); T2 = post-intervention (week 8); T3 = 1-month follow-up (week 12); T4 = 3-month follow-up (week 20).
mean difference = −1.15, %95CI = [−2.3,−0.01]). Although no difference was found in stimulant-positive urines in the whole sample, when only subjects with a history of methamphetamine use were compared, the CRT (n = 34) group had lower rates of amphetamine-positive urines than the control (n = 40) group, (CRT group = 1.53 ± 1.88, control group = 4.61 ± 3.49) [T = −4.28, p ≤ .01, mean difference = −3.07, %95CI = [−4.41,−1.63]) (Supplementary Figure 1).

To measure the effect size, we used Cohen’s d and interpreted the values according to Cohen (0.20 = small, 0.50 = medium and 0.80 = large) (Enz & Frosch, 2015). Analyses revealed the small to medium effect size in opiate use (d = 0.41) and large effect size in amphetamine use (d = 1.24).

**Outcomes at 6-month follow-up**

Due to the low rate of retention between the 3- and 6-month follow-up time points, analysis was performed and reported based on the data from 3-month follow-up (n = 23 and n = 28 for CRT and control group, respectively). Between 3- and 6-month follow-up assessment time points, 28 subjects (82% from the CRT and 78% from the control group) failed to complete assessments and 23 subjects (n = 10 and n = 13 for CRT and control group, respectively) remained in the study. Results showed no significant changes between 3- and 6-month follow-up time points for each group in terms of cognitive measures. Survival analysis using log-rank test indicates no significant difference between drop-out rate during study between the two groups (χ² = 1.29, p = .25)
The drop-out rate was higher during the first week after 3-month follow-up point, while, from 12 urine tests collected between 3- and 6-month follow-up, subjects in the CRT group had significantly lower rates of opiate use (0.35 ± 0.57) compared to the control group (2.78 ± 2.6) $[T = -4.28, p = .001, \text{mean difference} = -2.43, \%95CI = [-3.5,-1.2])$. Similar to what we had found at 1- and 3-month follow-up time points, subjects with a positive history of methamphetamine use in the CRT group had significantly lower rates of stimulant use than subjects in the control group (CRT group = 0.38 ± 0.51, control group = 2.787 ± 2.35) $[T = -3.57, p = .002, \text{mean difference} = -3.04, \%95CI = [-3.76,-1.01])$. No significant differences were found for number of missed sessions between the two groups (3.61 ± 5.1 for CRT group and 4.19 ± 5.1 for control group, $T = -0.45, p = .65$).

**Discussion**

The aim of the present study was to examine whether adding cognitive rehabilitation to an MMT programme could improve neurocognitive functions and improve substance use outcomes in subjects with opioid use disorder. Our results provide evidence that CRT may have beneficial effects on neurocognitive functions and substance use in subjects maintained on methadone. These beneficial effects remained durable up to 6 months after the subjects were discharged from the residential programme.

Consistent with previous reports (Alfonso et al., 2011; Bell, Laws & Petrakis, 2017; Goldstein, Haas, Shemansky, Barnett, & Salmon-Cox, 2005; Houben et al., 2011;
Rupp et al., 2012), we found that subjects who received CRT had a better performance in cognitive assessments compared to the control group. We found these improvements in learning, switching, processing speed, working memory and memory span tasks. Our results are consistent with the goals of the CRT intervention, which includes specific exercises to improve these cognitive functions; however, not all cognitive functions improved with CRT, including the performance in executive control, which was extracted from the Stroop test. Although the CRT group performed better than the control group for the Stroop, the difference was not significant. Another finding was that the changes in cognitive performance remained stable over the study duration in both CRT and control groups. These changes included the improvement in learning, switching, processing speed, working memory and memory span for the CRT group and in processing speed, switching and executive control for the control group. The control group also showed deterioration in performance of memory- and learning-related tasks, which was remarkable in different time points of assessment. These findings suggest that the neurocognitive gains achieved with CRT may be durable for at least 6 months. The durability of CRT on neurocognitive functions was previously reported for patients with schizophrenia over 12-month follow-up (Poletti et al., 2010) and for patients with depression over 3-month follow-up (Priyamvada, Ranjan, & Chaudhury, 2015).

CRT improved abstinence from drug use during the 6-month outpatient phase of the study. The CRT group had a lower number of positive urines for opiates and amphetamines compared to the control group. Our study was not designed and did not have sufficient power to address whether these improvements in drug use are mediated by improvements in cognitive function; however, we would like to suggest that these findings could be explained by the dual model of addiction, which proposes an imbalance between implicit and explicit systems in cognitive process. Enhancing the explicit system (top-down) through cognitive exercises could lead to better control over implicit (bottom-up) systems, which are responsible for impulsive behaviours (Houben et al., 2011; Sofuoglu et al., 2016). The beneficial effect of CRT on drug use has been previously reported only for those who use alcohol, not for those who use other substances (Houben et al., 2011; Sofuoglu et al., 2016); although, in a recent study, the combined effect of CRT and work therapy suggested an improvement to SUD outcomes in drug users, but the separate benefit of CRT has not been well-studied yet (Bell, Laws, & Petrakis, 2017).

Our study has several limitations that need to be addressed in future studies. First, we performed the CRT intervention in the court-mandated MMT centre, which is a residential programme, and followed subjects in outpatient settings for 6 months. The transition from residential to outpatient settings led to a high drop-out rate, especially at 6-month follow-up. We missed many subjects, especially after 3-month follow-up, which may be due to the fact that the legal follow-up period ended after the first 3 months after discharge. The high drop-out rate in this study may be also related to the emigration of subjects to other cities, to find a job or due to their re-involvement in illegal behaviours. Thus, results from the 6-month time point should be interpreted cautiously. Another limitation is that our sample consisted of men and did not include women subjects; this is an important limitation because gender could be a moderating variable for cognitive deficits in SUDs (Becker & Hu, 2008). The other noteworthy issue is related to the variables that are not our target in this randomised clinical trial. Urine drug tests for drugs other than methamphetamines and opioids (such as
benzodiazepines) or screening participants for other diseases (such as chronic human immune deficiency virus infection, hepatitis C, hypothyroidism and anaemia) that may contribute to cognitive decline could be considered in future investigations.

To the best of our knowledge this is the first study evaluating the effect of CRT in opioid users who are enrolled in MMT programmes over 6 months. Regardless of methodological limitations, our results support the feasibility and potential efficacy of cognitive rehabilitation to improve some neurocognitive functions and substance use treatment outcomes. These findings warrant further studies examining the role of CRT as an adjunct treatment in MMT programmes.

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Disclosure statement

The authors have no competing interests as defined by Neuropsychological Rehabilitation Journal Group, or other interests that might be perceived to influence the results and/or discussion reported in this article. The authors confirmed that no observations were excluded, all independent variables or manipulations, whether successful or failed, have been reported in the Methods section and all dependent variables or measures that were analysed for this article’s target research question have been reported in the Methods section.

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