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Baseline executive functions and receiving cognitive rehabilitation can predict treatment response in people with opioid use disorder

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Highlights:

- Assessment of executive function before MMT, may inform treatment providers about patient's cognitive deficits that may interfere with therapeutic interventions.
- Working memory and inhibitory control could be potentially considered as predictors of treatment response for newly MMT admitted patients with OUD.
- Using supplementary remediation interventions targeting different dimensions of cognitive functions including EF could promote treatment outcomes.

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Baseline executive functions and receiving cognitive rehabilitation can predict treatment response in people with opioid use disorder

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1. Introduction

Treatment success is a pervasive challenge discussed in the field of addiction treatment and reported among different treatment settings, especially for methadone maintenance treatment (MMT). Although MMT is one of the most commonly prescribed treatments for people with opioid use disorder (OUD)(Garcia-Portilla et al., 2014), research reports a high proportion of heroin-addicted individuals drop-out and relapse during the course of MMT (Lin et al., 2013). Limited and/or mixed evidence exists among studies reporting treatment success in this group of users, possibly due to a lack of agreement on defining criteria for treatment response (Bawor et al., 2015). However, decreased number of relapses and increased length of stay (retention) in treatment are the two most common measures associated with effective treatment (Craig & Olson, 2004; McHugh et al., 2013). Given the importance of effective treatment for substance users, a clear understanding of outcome predictors could lead to the application of more tailored therapeutic interventions that meet the need of people with substance use disorder (Carroll et al., 2011; Hogue et al., 2017). Some types of treatments require specific competencies that may be impaired in substance users. For example, for a person with poor concentration who is easily distracted by other people in a group, individual therapy sessions may be more effective.

Research on predictors of treatment outcome has identified a number of predictor variables commonly segregated into sociodemographic (i.e., employment status, history of injecting the drug of abuse); clinical (i.e., psychiatric conditions, previous head injury); psychological (i.e., craving, negative emotional states); and cognitive factors (i.e., executive functions, verbal skills) (Reske & Paulus, 2008; Teichner et al., 2001).

Cognitive deficits are among the most consistent risk factors for drop-out and subsequent relapses in substance users (Noel, 2002; O'Connor et al., 2020; Prosser et al., 2006; Shulman et al., 2018). Although the mechanism underlying this association is complex and still needs more clarification, some studies suggest that these cognitive deficits could compromise a person's ability to learn new skills and apply therapeutic strategies focused on skills-building and coping. In contrast, others argue that cognitive deficits may influence personal competencies (i.e., self-efficacy, motivation) that have a pivotal role in the mechanism of behavior change (Bates et al., 2004). Among various cognitive functions, executive function (EF) and directing goal-based behaviors are the topics of interest for many studies in the field of addiction treatment. Due to the correlation between EF and prefrontal structures, they are so vulnerable to drug effects (Brewer et al., 2008; Morgenstern & Bates, 1999). EF is a term used for higher-order cognitive functions that are linked to effortful processes including inhibition, working memory, and flexibility (Diamond, 2013). For people with SUD, EF impairments may lead to poor ability to change drug-seeking behavior (flexibility), to gain control over automatic drug-seeking behavior (inhibitory control), and to actively hold and update coping strategies to be used (working memory) in risky situations (Duijkers et al., 2016; Fino et al., 2014). EF measures are important in different processes of addiction, ranging from prevention to treatment (Grenard et al., 2008; Koob & Volkow, 2016; Pentz et al., 2016).

Taken together, addiction treatment could be influenced by various factors, including initial cognitive functions; however, limited evidence exists indicating whether using cognitive rehabilitation treatment (CRT) in combination with MMT could also predict treatment success in people with OUD. Therefore, in this study we hypothesized that people with higher baseline scores in EF measures and those who receive CRT as an adjunct intervention would be more likely to have better treatment response. This study used participants who had been recruited into a clinical trial (NECOREDA trial) comparing CRT with an active control intervention for people with OUD (Rezapour et al., 2015, 2019).

2. Method

2.1 Context of the current study: The original randomized trial

The current study tested some key variables for predictor effect within a comparative clinical trial of CRT for people with OUD who were court-ordered to receive MMT (Rezapour et al., 2019). The original trial recruited 120 patients and randomized these individuals into two groups (n=60 in each group). In the CRT group, participants received treatment as usual (TAU) plus a CRT program for sixteen, 1-hour sessions, while participants in the control group received the same number of sessions as the CRT group but engaged in painting. Primary and secondary outcomes were cognitive functioning and treatment outcomes over a 3-month follow-up, respectively. Our results indicated that the CRT group performed significantly better on tests of learning, switching, processing speed, working memory, and memory span. Moreover, the CRT group had a significantly lower relapse rate over the control group during a 3-month follow-up.

In addition, we found no significant group differences for treatment retention (Rezapour et al., 2019). The study matched both groups for demographic (i.e., age, years of education) and drug use (i.e., age at onset of opioid use, history of alcohol and methamphetamine) variables.

2.2 Eligibility criteria for the original trial

The original trial recruited participants in Iran between May 2015 and October 2016. They were all male, between 20 to 40 years old, fulfilled the DSM-5 criteria for OUD using the Persian version of DSM-5 checklist of symptoms (American Psychiatric Association, 2013), able to speak and write in Farsi fluently, and had signed informed consents prior to participating the study. The trial excluded participants if they had other major psychiatric (e.g., schizophrenia, bipolar disorder, or major depression disorder) or neurological disorders (e.g., head injury, epilepsy), had severe opioid withdrawal symptoms (as defined by the Objective Opioid Withdrawal Scale score > 6) at the end of the second week after admission, or reported a suicide attempt within the past month.

2.3 Interventions

- CRT group: The study conducted CRT in a group setting, as a 1-hour session two times per week over 8 weeks. The study applied CRT with the use of a developed NEuroCOgnitiveREhabilitation for Disease of Addiction (NECOREDA) program. NECOREDA is a paper-and-pencil training of cognitive functions that are commonly affected by SUDs, including attention, memory, calculation, visuospatial process, verbal skills, and reasoning (Rezapour et al., 2015). In addition to cognitive training, NECOREDA focuses on psychoeducational aspects of cognitive rehabilitation, including metacognitive education, and compensatory and lifestyle training.
- Control group: To minimize the plausible confounding effects of social interaction of the CRT, we used an active intervention for the control group. Participants in this group received 16, 1-hour group painting sessions. Previous studies have used painting as an active control intervention (Haimov & Shatil, 2013; Trapp et al., 2013).
- Treatment as usual (TAU): Both the CRT and control groups received TAU plus their CRT/ active control interventions. Similar to the routines of TAU in other court-mandated centers, the study provided participants with daily methadone prescriptions and counselling sessions. Methadone was started at 30–40 mg/day and individually titrated as needed, following the MMT guidelines in Iran. After the stabilization phase (at the end of the second week after admission), participants received a stable dosage of methadone, ranging from 60 to 70 mg/day, for 2 months, until the time of discharge from the center.

  After being discharged, participants received stable doses of methadone during the follow-up period, ranging from 90 to 100 mg/day, in an outpatient certified MMT program (National protocol published by Iran Ministry of Health for maintenance treatment of opioid users). According to MMT guidelines in Iran for residential MMT centers, after discharging from a residential center, physicians are allowed to increase the daily dose during the first 10 days (3 mg per day) as a person reaches a stabilized condition. During the follow-up period, participants only received their daily methadone as medication and basic psychosocial interventions in outpatient methadone clinics.

2.4 Assessments and analysis

A trained clinical psychologist administered all the measures below at the end of the second week of admission prior to CRT or control intervention, except the Objective Opiate Withdrawal Scale, which they administered at the end of the first week of admission as well. The psychologist also administered follow-up measures weekly during the 3-month follow-up.

2.4.1 Instruments

- Participants self-reported demographic variables, including participants' age, marital status, and years of education.
- Using a structured interview, based on the clinical drug addiction profile (CDAP) (Mokri et al.,2012), study staff collected drug use variables (opioid use duration, age at onset of nicotine use, lifetime history of methamphetamine and alcohol).
- The study administered the Beck Depression Inventory (BDI) to screen symptoms of depression. The BDI is a self-report instrument consisting of 21 items representing a symptom related to depression (e.g., guilt, loss of interest). All items are rated on a four-point scale from 0 (the absence of a given symptom) to 3 (maximum level of severity). The sum of 21 items (ranging from 0 to 63) represents the BDI total score. Scores above 30 indicate severe depression and are considered as a cut-off point to exclude participants (Olaya-Contreras, 2010). We used the Persian version of the BDI, which research has shown to have high internal consistency (Cronbach's alpha=0.87) and acceptable test-retest reliability (r=0.74)(Ghassemzadeh et al., 2005). The main purpose of utilizing the BDI in this study was to control for the confounding effect of depression on the neurocognitive functions (Tate et al., 2011).
- A physician used the Objective Opiate Withdrawal Scale (OOWS) to monitor the presence and intensity of withdrawal symptoms (e.g., hand tremors, vomiting) at the first and second week of admission (Tompkins et al., 2009; Zarghami et al., 2012). The OOWS comprises 13 physically observable signs, rated present (score=1) or absent (score=0), based on a timed period of observation of the patient by a clinician. The total score is the sum of all scores. Higher scores are associated with a more severe withdrawal syndrome. For the current analysis, we used the average score of the first- and second-week scores.

- Executive functions measures:

1. Working memory: To assess working memory, we used word span measure from the Ray Auditory Verbal Learning Test (RAVLT)(Bleecker, 2005) and Backward Digit Span Test (BDST)(McAvinue et al., 2013). Although both tests measure verbal working memory, the RAVLT mainly measures working memory capacity for meaningful items and is usually taken to evaluate compensatory memory strategy training. In the RAVLT, the study staff read a list of 15 words for the participants with a presentation rate of one word per second. After the presentation of the list, study staff asked the participants to freely recall as many words as possible. We should note that we used the Persian version of the test in this study with reliability value ranges between 0.56 to 0.70 (Rezvanfard et al., 2011). The BDST consists of a variable sequence of random digits (1–9) that was read aloud for the participants at a rate of one digit per second. The participants then repeat the sequence in the reverse order immediately after it is

presented. Each item has two trials with digit sequences of the same length, starting from 2 digits (first item) and proceeding to 10 digits (last item). The test gets progressively more difficult by increasing the number of digits, and the test is terminated if both trials of a test item are repeated incorrectly. We used the Persian version of the BDST validated for the Iranian population (internal consistency ranged between 0.77 to 0.88)(Mohammadi et al., 2014). The study defined the number of correctly recalled words in the RAVLT and the number of sequences repeated correctly in the BDST as the measures of working memory.

2. Inhibition: To assess inhibition, we used the Stroop task (Dodrill's version) in a paper-and-pencil version (Diamond, 2013). In this test, the study staff presented participants with a list of 176 color words from four colors (red, yellow, green, blue), which were written in nonmatching color ink. In the first part, the participants had to read the color words while ignoring the ink color, and in the second part, study staff asked them to name the ink color of the word. We include in the analysis the Stroop Color-Word Test (SCWT) Interference score, measured by the time difference between the two parts (Sacks et al., 1991). We used the Persian version of the Stroop task adapted to the Iranian population, which research has shown to have internal consistency of 0.83 and 0.97, for reaction time in each part, respectively (Saremi et al., 2017)
3. Shifting: To assess shifting, we used the Trail making task (A and B) (Muir et al., 2015). In part A, study staff asked participants to connect 25 circles numbered from 1 to 25 with lines as quickly as possible. While, in part B the participants were asked to connect circles containing numbers (from 1 to 13) or letters (from A to L) in an alternate numeric/alphabetical order as quickly as possible. The TMT A-B score is calculated as the difference between TMT-A and TMT-B times as a measure of flexibility. The TMT has a high coefficient of reliability [Part A; r=0.79; Part B: r=0.89](Miskin et al., 2016) and is broadly used for Farsi-speaking people (Batouli et al., 2021).

- Treatment response measures

Treatment response measures included retention and the relapse rate over a 3-month follow-up. The study quantified treatment retention based on the week participants have dropped out. For example, the considered a participant to have dropped out if he missed two consecutive visits. The study defined relapse rate as the number of positive urine analysis results for morphine. During the follow-up period, all participants had to come to the MMT clinic to receive methadone twice a week (24 visits for each participant) and provide a urine sample (12 urine samples for each participant). The study considered a missed urine test prior to study drop-out as positive for opioid use when summarizing abstinence (Pan et al., 2015).

2.4.3 Data analyses

We estimated that a sample of 120 participants would provide a power of 0.80 to detect a medium effect size for measures of cognitive functions, which was previously reported by Rupp and colleagues (Rupp et al., 2012), based on a p-value of 0.05, with 45% expected attrition rate. To characterize the sample, first, we descriptively analyzed the distribution of demographics, drug use, and EF-related variables, using numbers and percentages to describe categorical variables, and using mean and standard deviation (SD) to describe quantitative variables.

Second, we conducted a survival analysis using Cox's proportional hazards model to examine the impact of years of education, EF measures, and intervention group (CRT vs. active control) on the week participants dropped out of the study. The study coded control (as the *reference group*) and CRT intervention groups as 0 and 1, respectively. Third, we used the linear mixed model (LMM) to assess the effect of EF measures and intervention group on the number of positive urine test results. Last, we conducted exploratory independent-samples t-tests to examine whether baseline scores in EF measures and the number of positive urine test results are different between participants with/without a history of alcohol and methamphetamine. We performed all statistical analyses using SPSS Statistics 23 (IBM, Chicago, IL), and set the level of significance at ≤ 0.05.

2.4.4 Governance

The independent ethics committee of the University of Social Welfare and Rehabilitation Sciences (USWR), Iranian Ministry of Health (code USWR.1393.161) approved the NECOREDA study.

3. Results

3.1 Descriptive analysis

Of 120 participants who met all inclusion criteria, 117 completed pre-assessments and we randomly assigned them to receive CRT plus TAU or active control intervention plus TAU for 8 weeks. A total of 113 participants completed post-assessments and the study followed them over 3 months. The CONSORT flow diagram (Figure 1) shows the number of participants attending and providing data at each stage of the trial. Study staff analyzed data collected during the follow-up period for this secondary analysis. All participants were men with a mean age of 32.09 years (21-40 years). They were all daily smokers, and 64.1% started using opioids before age 20. Table 1 provides the baseline characteristics of all participants.

Insert Figure 1

Insert Table 1

3.1.1 Survival analyses

Of 113 participants who attended the follow-up stage, 62 (54.86%) dropped out of treatment over 3 months. The study used Cox proportional hazards regression model to predict time to drop-out during the 3-month follow-up (12 weeks), with years of education, group intervention, and baseline EF measures. The study found the model to be significant (−2 log-likelihood = 480.079, $\chi2 = 33.15$, df = 6, P <0.001). Of the variables entered into the model, the SCWT interference score was significantly related to the length of stay (Table 2). More specifically, hazard ratio (HR) suggests that participants who achieved higher SCWT interference scores tended to exhibit a greater level of hazard for drop out, meaning lower survival times until drop out (HR = 1.01, p<0.001). Given the effect of the SCWT interference score on the hazard of drop-out, the study classified participants as having high SCWT interference scores, if their scores were higher or equal to the median (89) and coded as 1, while the study coded those with scores lower than 89 (coded as 0) as having a low SCWT score. The study plotted the Kaplan–Meier survival curves according to the categories of high and low SCWT interference scores (Figure 2).

Insert Table 2

Insert Figure 2

3.1.2 Linear mixed model

During a 3-month follow-up, the mean number of positive urine test results from 102 participants was 2.93 (2.94). Table 3 summarizes the results of the LMM for positive urine tests. We found a significant effect for intervention (β=1.30, p = 0.02), and a significant effect for RAVLT score (β= –3.02, p < 0.0001). The Control group had positive urine tests that were, on average, 1.30 times more than the CRT group. During a 3-month follow-up, we also found that the number of positive urine tests increased with decreasing RAVLT scores.

Insert Table 3

3.1.3 Exploratory analysis

Exploratory analyses between participants with and without a history of methamphetamine use indicated no significant subgroup differences on baseline EF measures and number of positive urine test results (Table 4). While, in comparison to those with a positive history of alcohol use, the other group indicated a significantly higher score in BDST (t=2.20, p=0.03) and lower interference score in SCWT (t= –2.28, p=0.02) (Table 5).

Insert Table 4

Insert Table 5

4. Discussion

The study team conducted the current secondary analysis of NECOREDA to examine predictors of treatment response in participants with OUD who were admitted to an MMT program and provided with supplementary cognitive rehabilitation or active control interventions. We found that lower inhibition was predictive of decreased treatment length of stay. Furthermore, we found that receiving an adjunct cognitive rehabilitation program and higher working memory capacity (for meaningful items) were associated with decreased number of positive urine tests. Our findings are in agreement with several other studies indicating the role of cognitive performance indices in predicting treatment response in substance and alcohol use disorders (Ersche & Sahakian, 2007; Shulman et al., 2018; Verdejo-García et al., 2012).

Poor treatment retention is a serious challenge for addiction treatment programs that frequently encounter early drop-out and irregular attendance. Our findings point out that participants who had higher interference scores in the Stroop test (poor inhibition) were more likely to drop out and terminate treatment. Results from previous studies revealed that the Stroop test is a proper index of the ability to suppress a habitual behavior in favor of an opposing goal-directed response (Kane & Engle, 2003). In the context of addiction recovery, the habitual drug use response is associated with treatment drop-out, whereas the goal-directed response could be reflected in treatment retention (Streeter et al., 2008).

The number of positive urine drug tests is a crucial measure of treatment outcome. In the current study, participants in the CRT group and those with a higher capacity of working memory (assessed with words as meaningful items) were less likely to relapse. Relapse is a core characteristic of addiction that requires complex cognitive processes used to cope and exert control. Higher baseline working memory and improved cognitive functions (including learning, switching, processing speed, working memory, and memory span) as a result of receiving CRT (reported in the main study) could help participants to efficiently use these cognitive processes to access their relapse prevention skills (learned during TAU) and other helpful cognitive resources to cope with craving and subsequently reduce the risk of relapse. The role of working memory in successful self-regulation has been observed in studies using working memory training in drug users (Bickel et al., 2014). For example, Bickel and colleagues reported a significant increase in self-control and valuation of delayed rewards in the group receiving working memory training sessions (Bickel et al., 2011).

Of note, our findings did not indicate a significant role of shifting in predicting treatment response. This result is consistent with a previous study from Aharonovich and colleagues (Aharonovich et al., 2006), which indicated a nonsignificant relationship between users' performance in shifting demanding tasks and treatment outcomes. We assume that it may be due to the test that we used for measuring shifting (Trail Making Test), which might not be sensitive enough to detect impairments in shifting in substance users.

In this study, we also found that participants with a history of alcohol use achieved lower scores in the BDST (the measure of working memory) and higher scores in the Stroop task (the measure of inhibition) compared to nondrinking participants. Our results are consistent with many studies that have reported an association between increased alcohol use and deficits in working memory and inhibition (Gan et al., 2014; Martins et al., 2018; Parada et al., 2012). The poorer performance in the BDST and Stroop task indicates that alcohol consumption is associated with a lower capacity of working memory to retain and manipulate verbal information and lower control to inhibit the prepotent behavioral response. We did not find any significant difference in the RAVLT and TMT, which may be due to the low sensitivity of these tests to detect alcohol-related problems. Moreover, we did not find a significant difference between participants with and without a history of methamphetamine use in different measures of EF. Although we did not collect detailed data, we assume that the intensity and frequency of methamphetamine consumption in the users' group may be less than the level needed to make a statistically considerable difference.

Although various studies have indicated the role of baseline cognitive functions in predicting addiction treatment outcome, our study is among the first to indicate that adding cognitive rehabilitation treatment to MMT could predict improved treatment outcomes. One of the limitations in the current analysis is related to a long list of potentially important confounders (e.g., degree of polysubstance use, social support, and deprivation, treatment readiness) that this study did not assess. We also did not measure IQ directly in this study; although prior studies have considered it to be associated with addiction treatment outcomes (Kiluk et al., 2010). Nevertheless, we measured other neuropsychological factors (i.e., working memory, attention) that were specifically targeted in the CRT program to see whether they would change over the course of the intervention. We also included years of education in our current analysis, which is known to correlate with IQ (Ritchie & Tucker-Drob, 2018) and so could potentially affect participant’s ability to learn and use the provided therapeutic information. However, we did not find any significant effect of years of education in predicting treatment responses.

Another limitation is that, in the main trial, we recruited people who entered the MMT program with OUD as their main substance use disorder, while they might have a positive history of other drugs, including methamphetamine and alcohol. During follow-up sessions, our primary goal was to monitor MMT success in terms of reduced relapse rates to opioids. So, we used single drug dipstick urine tests for morphine and methamphetamine (due to the high drop-out rate of participants with a positive history of methamphetamine, we could not consider their data in the current analysis). Some synthetic opioids may not have been detected with the morphine test, which future studies should consider.

The final limitation is that we recruited only male users. This limits our ability to generalize the results to females, as some evidence indicates gender differences as a risk factor for substance use (Manchikanti & Singh, 2008; Osborne et al., 2017). Future research should take all these limitations into account. Nevertheless, this study does provide some preliminary evidence for the predictor role of receiving adjunct CRT and baseline executive function in treatment responses in a less-studied clinical context.

This study highlights cognitive risk factors for lower treatment response and addresses the importance of using cognitive assessments before initiating treatment. These assessments could inform treatment providers about the severity of cognitive impairments, which may interfere with the process of recovery and hinder treatment progress. The cognitive profile of patients could also influence the type/module of treatment that providers use, because treatment success may depend on different cognitive processes. For example, when using verbal instruction, a participant's low verbal memory could interfere with treatment outcomes if patients cannot properly learn and remember the verbally presented material. Moreover, our findings support the idea of using supplementary remediation interventions targeting different dimensions of cognitive functions (Ersche & Sahakian, 2007; Sofuoglu et al., 2016; Verdejo-Garcia, 2016). Few studies exist that indicate promising results of using specific cognitive remediation focused on working memory and inhibition training (Bickel et al., 2011; Houben et al., 2011, 2012; Rass et al., 2015) or more general multi-component cognitive remediation interventions (Ekhtiari, Hamed, 2017; Gamito et al., 2017; Rupp et al., 2012) and how these relate to treatment outcomes. Adjusting therapeutic interventions according to an individual's cognitive control profile is a promising approach both for future studies and clinical settings.

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Contributors

TR, HE, MS, and RD designed the procedure. TR, HE, JH, AF, and AB contributed to the analysis. TR, HE, and AN ran the study. All authors participated in the writing and revising of the manuscript.

Conflict of Interest

The authors have reported no conflict of interest.

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Table 1: Baseline characteristics of total participants entered into the study (2 months residential and 3-month follow-up).

	Total sample (n=117) **Mean (SD)**
Age (years)	32.09(6.20)

Years of education	8.79(2.28)
Opioid use duration (years)	13.44(6.26)
Age at onset of nicotine use	17.56(4.93)
Opioid withdrawal severity score	3.63(2.85)
Beck Depression Inventory score	28.85(10.85)
RAVLT (word span)	5.85 (2.22)
SCWT, time inference (sec)	99.16 (41.02)
BDST (item)	3.88 (1.11)
TMT 'B-A' (sec)	60.17 (44.79)
	N (%)
Marital status	
Married	41(35)
Single	76(65)
Positive history of other substances (life-time)	
Methamphetamine	74(63.2)
Alcohol	30(25.6)

Note. RAVLT=Rey Auditory Verbal Learning Test; SCWT=Stroop Color-Word Test; BDST=Backward Digit Span Test; TMT=Trail Making Test

Table 2: Parameter estimates, confidence intervals, and tests statistics from Cox proportional hazards regression analysis predicting time to drop-out during the 3-month follow-up.

Variable	HR	95% *CI* (Lower, Upper)	Wald χ2 *(df=1)*	*p*
Intervention group*	0.62	0.36,1.07	2.94	0.08
RAVLT (word span)	1.03	0.91,1.16	0.26	0.60
SCWT, time inference (sec)	1.01	1.009,1.02	20.49	*<0.001*
BDST (item)	0.82	0.64,1.05	2.45	0.11
TMT 'B-A' (sec)	0.99	0.98,1.003	1.57	0.21
Years of education	0.92	0.81,1.06	1.15	0.29

*Note. Intervention group coded 0 for the control group and coded 1 for CRT group; RAVLT=Rey Auditory Verbal Learning Test; SCWT=Stroop Color-Word Test; BDST=Backward Digit Span Test; TMT=Trail Making Test

Table 3: Linear mixed-effects model.

Variable	Estimates (SE)	Test (df)	95% *CI* (Lower, Upper)	*p*
Intervention group*(reference=control)	1.30 (0.56)	2.31 (95)	-2.43, -0.18	*0.02*
RAVLT (word span)	-0.41(0.13)	-3.02(95)	-0.69, -0.14	*P<0.001*
SCWT, time inference (sec)	-0.002 (0.007)	-0.38(95)	-0.018,0.012	0.70
BDST (item)	-0.17 (0.25)	-0.67(95)	-0.67,0.33	0.50
TMT 'B-A' (sec)	-0.006 (0.007)	-0.83(95)	-0.020,0.008	0.40
Years of education	0.24 (0.13)	1.86(95)	-0.01,0.51	0.06

*Intervention group, coded 0 for control group and coded 1 for CRT group; RAVLT=Rey Auditory Verbal Learning Test; SCWT=Stroop Color-Word Test; BDST=Backward Digit Span Test; TMT=Trail Making Test

Table 4: Comparison of baseline EF measures and positive urine test results between participants with and without history of methamphetamine use.

Variables	Groups	Mean (SD)	95% *CI* (Lower, Upper)	t	*p*
RAVLT (word span)	Positive (n=43)	5.93 (2.10)	-1.05,0.63	-0.49	0.62
	Negative (n=74)	5.72(2.42)			
SCWT, time inference (sec)	Positive (n=43)	100.55(46.26)	-19.42,11.84	-0.48	0.63
	Negative (n=74)	96.77(30.29)			
BDST (item)	Positive (n=43)	3.95(1.21)	-0.60,0.24	-0.83	0.40
	Negative (n=74)	3.77(0.92)			
TMT 'B-A' (sec)	Positive (n=43)	61.52(48.43)	-20.73,13.40	-0.42	0.67
	Negative (n=74)	57.86(38.13)			
Positive urine test results	`Positive (n=63)	2.76(2.97)	-0.75,1.63	0.73	0.46
	Negative (n=39)	3.21(2.92)			

Table 5: Comparison of baseline EF measures and positive urine test results between participants with and without history of alcohol use.

Variables	Groups	Mean (SD)	95% *CI* (Lower, Upper)	t	*p*
RAVLT (word span)	Positive (n=30)	5.90(2.09)	-0.99,0.87	-0.12	0.89
	Negative (n=87)	5.84 (2.27)			
SCWT, time inference (sec)	Positive (n=30)	113.63(53.91)	-36.36, -2.56	-2.28	0.02
	Negative (n=87)	94.17 (34.51)			
BDST (item)	Positive (n=30)	3.50(0.97)	-0.05,0.97	2.20	0.03
	Negative (n=87)	4.01(1.13)			
TMT 'B-A' (sec)	Positive (n=30)	68.30(58.01)	-29.67,7.83	-1.15	0.25
	Negative (n=87)	57.37(39.24)			
Positive urine test results	Positive (n=24)	3.21(3.34)	-1.73,1.01	-0.52	0.60
	Negative (n=78)	2.85(2.83)			

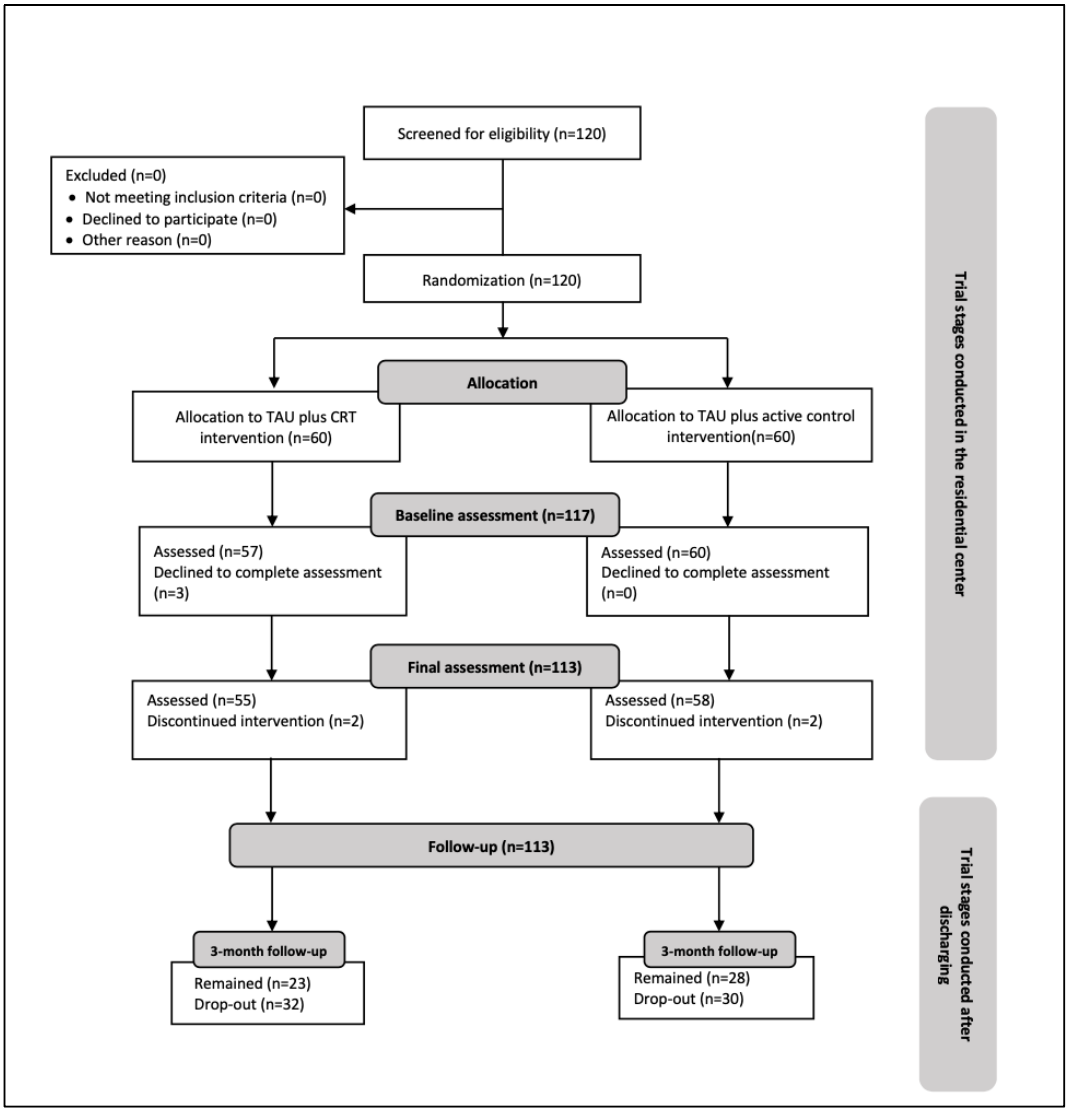

Figure 1: CONSORT flow diagram.

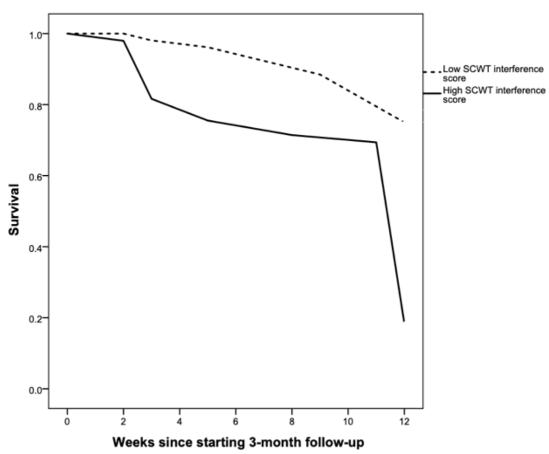

Figure2: Kaplan-Meier survival of time to out drop by low and high Stroop color-word test interference scores.

Author statement

TR, HE, MS and RD designed the procedure. TR, HE, JH, AF and AB contributed to analysis. TR, HE and AN ran the study. All authors participated in the writing and revising of the manuscript.