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Cognitive Functioning and Treatment Outcomes in a Randomized Controlled Trial of Internet-delivered Drug and Alcohol Treatment

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Abstract

Background: Substance use disorders are associated with lower cognitive functioning, and this impairment is associated with poorer outcomes. The Therapeutic Education System (TES) is an internet based psychosocial intervention for substance use disorders that may provide enhanced treatment for individuals with cognitive deficits. This secondary analysis investigates the association between cognitive functioning and treatment outcomes in a large (N=507) randomized controlled effectiveness trial of TES compared to treatment-as-usual conducted within outpatient programs in the National Drug Abuse Treatment Clinical Trials Network.

Methods: All participants completed a computer-based cognitive assessment (Microcog™ short version) at baseline. Scores on subtests of attention, reasoning, and spatial perception were tested as moderators of the treatment effect on abstinence and retention at the end of the 12-week treatment phase using mixed effects logistic regression.

Results: Cognitive functioning was not found to be a moderator of treatment on abstinence or retention. Post-hoc analysis of the main effect of cognitive functioning on retention and abstinence found impaired reasoning and cognitive flexibility were associated with lower retention. There were no other main effects of cognitive functioning on retention or abstinence.

Conclusions: The benefit of internet delivered treatment over standard care was unchanged across a range of cognitive functioning. Consistent with previous research, mild to moderate impairment in reasoning and cognitive flexibility were associated with lower retention across both treatment arms.

Scientific Significance: An internet-delivered cognitive behavioral intervention for substance use disorders, TES, is equally effective across a spectrum of cognitive functioning among diverse patients.

Mesh Terms:

Substance Use Disorders; Cognitive Disorders; Cognitive Functioning

Introduction

Individuals with substance use disorders have significantly lower scores on cognitive testing when compared to the general population^{1–5}. Further, cognitive impairment is associated with poorer outcomes suggesting that interventions which are compatible with a broad range of neuropsychological function are necessary⁶.

One promising approach is to leverage technology to deliver treatment in a manner that is appropriate for individuals with cognitive dysfunction. Several computer-assisted, internet delivered interventions for substance use disorders have been developed and tested^{7–10}. These interventions provide quality controlled evidence-based psychosocial interventions which are potentially scalable and may also provide a benefit to individuals with cognitive impairment by allowing for individualized learning, greater flexibility, and ongoing assessment of content mastery.

The “Therapeutic Education System” (TES), approved by the FDA in September 2017 as the first mobile medical application for the treatment of SUD¹¹, is an Internet-delivered psychosocial intervention grounded in the Community Reinforcement Approach (CRA) and often used in conjunction with automated contingency management⁸. The TES program uses “fluency-based” Computer-Assisted Instruction (CAI), a way of teaching information and skills that promotes retention of new information¹². This instruction requires patients to achieve mastery of material to progress. Mastery is evidenced by accuracy and speed of response on exercises, promoting active participation by the patient⁸. Experiential learning environments are included via interactive videos of actors modeling important skills (e.g., progressive muscle relaxation, drug refusal skills) to further engage the patient in thinking through real-world scenarios.

TES has been shown to be superior to standard care among methadone patients (N=160) with impaired attention/mental control, memory, information processing accuracy or general cognitive functioning¹³. In those assigned to standard care the cognitively impaired subgroup had lower rates of abstinence compared to those without cognitive impairment, but no such differential response was found in the group receiving TES.

This improved response among those with cognitive impairment was not found in a trial (N=77) in the general substance use population of a second technology based intervention, CBT 4 CBT, using other cognitive testing of intelligence, attention, processing speed and impulsivity. That CBT 4 CBT study did find that greater impulsivity as measured by a virtual test of impulse control correlated with poorer retention and increased drug use only in the intervention arm¹⁴.

In light of the above results showing possible added benefit of internet delivered treatment for individuals with low cognitive functioning and substance use disorders, the current study

set out to examine cognitive functioning as a moderator of treatment outcome in a large randomized controlled effectiveness trial. The primary outcome of this trial found that TES was superior to treatment as usual on abstinence and retention outcomes and this finding was especially prominent among those who were not abstinent at baseline assessment. The current exploratory secondary analysis of cognitive functioning as a moderator of treatment response adds to previous work in this area in that the trial included a diverse community sample recruited from 10 outpatient treatment locations throughout the United States and was not restricted to individuals with a specific alcohol or drug use disorder. The trial did exclude individuals who were currently prescribed opioid maintenance therapy. We set out to replicate the finding of a significant moderation effect between TES and cognitive impairment, whereby individuals with greater cognitive impairment would have better treatment outcomes in the TES condition compared to standard care only.

Methods

Initial Study Design

Details of the methods of this study and primary outcomes have previously been published⁷. Briefly, the study was a randomized controlled trial for patients (N=507) seeking treatment for drug or alcohol problems at 10 community-based, outpatient treatment programs across the United States. Patients were eligible if they were age 18 or older, reported illicit substance use in the 30 days before study entry and were within the first 30 days of their current treatment episode. Patients were excluded if they were currently prescribed opioid maintenance therapy (i.e., buprenorphine or methadone). Patients were randomized in a 1:1 ratio to receive 12 weeks of either: (1) treatment-as-usual in their outpatient treatment program; or (2) treatment-as-usual plus the Therapeutic Education System (TES) and automated contingency management. The TES intervention was a substitute for approximately 2 hours per week of clinician-delivered treatment-as-usual (the equivalent of 4 TES modules or topics per week).

Intervention

The Therapeutic Education System (TES) includes 62 interactive, multi-media modules grounded in the Community Reinforcement Approach (CRA), plus contingency management. The CRA consists of education and skills training to increase drug-free activities and to improve interpersonal interactions¹⁵. TES modules include training on basic cognitive behavioral relapse prevention skills (e.g. drug refusal, managing thoughts about using, conducting functional analyses), additional skills aimed at improving psychosocial functioning (e.g. communication, mood management, family/social relations, time management), as well as prevention of HIV, hepatitis and other sexually transmitted infections. The modules also included video clips showing actors modeling the skills being taught and short quizzes that assess grasp of the material to ensure content mastery before moving to the next module. The pace and level of repetition of material is adjusted to maximize individual mastery of the skills and information being taught. Patients accessed modules on computers provided at the treatment program or offsite at a location of their choice.

TES includes a flexible system for delivering contingency management using a prize-based incentive system that has been demonstrated to be effective in improving outcomes¹⁶. Incentives take the form of opportunities to draw vouchers from a virtual “fish bowl”. Vouchers yield congratulatory messages (e.g. “good job”) about half the time, or prizes of mostly modest value (usually around \$1, occasionally around \$20, rarely \$80-\$100). In the present study, draws were awarded for abstinence, measured by negative urine or alcohol breathalyzer screens, and for completion of modules (up to the recommended 4 per week although there was no cap on the number of modules that could be completed).

Drug/Alcohol Abstinence Assessment

Participants self-reported their primary substance of use (i.e., the substance for which they were seeking treatment or considered the most problematic). Abstinence from drugs was assessed via urine collected and screened for 10 drugs with standard lateral flow chromatographic immunoassays (QuickTox[®] dip card). Abstinence from alcohol was assessed via breathalyzer and self-report using the Timeline Follow-back method¹⁷. The outcome measure abstinence was defined as abstinence from all drugs and alcohol over the final four weeks of the study, allowing for up to two (of eight) half-weeks of missing data per subject. Subjects with more than two half-weeks of missing data were considered non-abstinent.

Neuropsychological Assessment

The MicroCog[™] computerized assessment of cognitive functioning is an age and education normalized and standardized cognitive assessment for a nationally representative sample of adults¹⁸. Based on our previous work with neurocognitive testing and treatment outcomes, a shortened version of the MicroCog[™] (20–25 minutes in length; 8 sub-tests) was used. The subtests measured three cognitive domains: attention/mental control, reasoning, and spatial processing, and were chosen because they had been shown in previous work to be more sensitive in predicting poor treatment outcomes¹⁹.

Attention and mental control refers to the ability to attend to new information and to store and mentally manipulate this information in the short-term. This area of function was measured using the *Numbers Forward* and *Numbers Reversed* subtests. These tests asked participants to recall digit spans, either forward or reversed. The *Wordlist 1* and *Wordlist 2* subtests were used to test incidental verbal learning, or memory for words presented without initially being prompted to recall them.

The reasoning domain was measured via the *Analogies* subtest, a test of the individuals’ ability to connect new ideas with information they have already learned. Also included in this domain were the *Object Match A* and *Object Match B*, measures of cognitive and conceptual flexibility and abstraction; that is, an individual’s ability to shift their thinking to patterns or ideas.

Finally, spatial processing was evaluated using the *Clocks* subtest, a test showing analog clocks hands, asking subjects to transform the time to digital representation. This measures spatial processing and executive functioning abilities²⁰.

Subtest raw scores based on total correct response were transformed to population based scaled scores (mean = 10.0, sd = 3.0). Clinically significant impairment was defined as being more than one standard deviation below the mean. Proficiency scores were also calculated for six of eight subtests using a combination of measured accuracy and speed, with greater weight given to accuracy.

Statistical Analysis

Mixed effects logistic regression models were used to examine the moderating effect of the eight cognitive assessment subtests on treatment effect (treatment-as-usual vs. TES) by examining the interaction between the subtest scores and treatment arm on two outcomes: abstinence (yes or no in the last 4 weeks of treatment) and treatment retention at the end of the 12-week treatment phase (yes or no). Cognitive subtest scores were examined as continuous variables and as dichotomized variables whereby individuals were categorized as impaired (cognitive scores more than one standard deviation below the population based mean) or not impaired. The model controlled for baseline abstinence (yes or no based on urine drug screen and alcohol breath screen) and site was treated as a random effect. Separate analyses were performed for each cognitive subscale measure for both total and proficiency scores and separately for both abstinence and treatment retention.

When the interaction term was not significant, a logistic regression analysis was conducted post-hoc to explore the main effect of cognitive functioning. All analyses were conducted using SAS 9.4.

Results

The baseline characteristics of the two groups, TAU and TAU+TES, are displayed in Table 1. Further demographic details are provided elsewhere²¹. In brief, the sample was 38% females and a majority identified as White (56%) or Black/African American (23%) and approximately 11% identified as Hispanic. Subjects included relatively equal numbers of individuals seeking treatment for alcohol, cocaine, cannabis, and heroin, with slightly fewer individuals seeking treatment for stimulants. Sixty percent of the sample had graduated high school, fifteen percent completed some post high school education and forty percent were employed.

Cognitive Impairment as a Moderator of Treatment

In the mixed effect logistic regression models controlling for baseline abstinence, no interaction terms (treatment arm by cognitive assessment subtest) were significant on either retention or abstinence (See Table 2). That is, none of the cognitive subtests (total score or proficiency scores) moderated the treatment (treatment-as-usual vs TES) effect on the outcome of abstinence in last four weeks of treatment or retention in treatment at the end of the 12-week treatment phase.

We also explored the moderation effect of dichotomous cognitive subtest scores (impaired vs not impaired). Cognitive impairment was not a significant moderator of the treatment effect on either outcome.

Main effect of Cognitive Impairment

Analysis of the main effects of continuous cognitive functioning subtest scores on abstinence and retention, controlling for baseline abstinence, showed that subtests of attention, mental control, and spatial processing were not significantly associated with abstinence nor retention at end of treatment (see Table 3).

However, several subtest scores in the domain of reasoning were significantly associated with retention (Table 3). When adjusted by baseline abstinence, analogies total score ($P=.008$; OR=1.09, 95%CI:1.02–1.17) and proficiency score ($P=.011$; OR=1.11, 95%CI:1.03–1.21) was significantly associated with retention, as was object match A ($P=.023$; OR=1.06, 95%CI:1.01–1.11) and object match B ($P=.02$; OR=1.07, 95%CI:1.01–1.14). For all significant main effects of the subtest scores, higher cognitive functioning (higher scores) were associated with greater treatment retention. Odds ratios refer to the increased odds of retention for each additional point on the cognitive subtest. None of the reasoning subtests were associated with the abstinence outcome.

Discussion

In this exploratory secondary analysis of a large randomized controlled trial of an Internet-delivered psychosocial treatment, cognitive functioning did not moderate the treatment effect on the outcomes of abstinence at the end of treatment or on retention. Thus, the hypothesis that TES might be especially effective among patients with lower cognitive functioning was not confirmed. Instead, the findings suggest no evidence that TES differs in its effectiveness across levels of cognitive function, and is therefore an appropriate treatment for patients with cognitive impairment.

The finding that cognitive functioning did not moderate the effect of an internet delivered treatment differs from a prior trial of TES which, unlike this trial, was performed in a methadone maintenance treatment setting. That trial found a significant interaction between Microcog scores and treatment (TES vs TAU) on percentage of total weeks with continuous abstinence and percentage of tested weeks with continuous abstinence. In that trial Microcog scores predicted abstinence in treatment as usual group but did not show similar predictions in the TES arm¹³. Differential findings may be due to variation in the study samples, as the previous trial only included individuals in methadone maintenance programs while the current study only included patients in general outpatient addiction treatment programs. Individuals in methadone maintenance programs differ significantly from the general population included in the current study in that all have opioid use disorder, generally this disorder is severe, and are all maintained on medication assisted treatment

Our findings are consistent with previous research by Carroll and colleagues who found that cognitive impairment did not moderate the effect of a computer-assisted cognitive behavioral therapy for substance use disorders on abstinence and retention¹⁰. Both studies were similar in including individuals seeking outpatient treatment not on medication assisted opioid maintenance treatment.

The implication of these findings are important in that it appears that individuals with clinically significant cognitive impairment derive similar benefit from internet-based interventions compared to those with normal cognition, even among a broad sample of individuals presenting to community-based addiction treatment.

The finding that cognitive impairment does not preclude use of technology-based interventions has been supported in other clinical areas as well. Internet delivered treatments have been found to provide equal benefit regardless of education history in the areas of depression and transdiagnostic symptom severity after hospital discharge^{22,23}.

More research is needed to determine if there are ways to leverage technology-based interventions to be more effective for those with lower levels of education or greater cognitive impairment. For example, future work might explore ways to more effectively use technology-based interventions for individuals with cognitive impairment. These interventions are by design completed independently with minimal oversight by clinical staff, something that might be problematic for individuals with cognitive impairment. It may be difficult for these individuals to focus and engage in treatment without the presence of a provider. Verbal and reading deficits may also create difficulty in understanding and absorbing the material. Future interventions might track eye movements or add continuous verbal response requirements throughout the intervention to monitor and maintain patient focus. In addition, future research is needed to identify thresholds by which technology-based interventions may not be indicated based on cognitive impairment.

This study partly replicated prior findings showing that cognitive functioning is associated with treatment retention as a main effect. Our group was among the first to identify an adverse impact of cognitive functioning on outcomes in individuals treated with CBT based relapse prevention therapy. Impairment in the domains of attention, memory, spatial ability, speed, accuracy, global cognitive functioning and global proficiency were associated with lower treatment retention¹⁹. In contrast to this previous study, the present study showed no association between cognitive impairments and decreased retention, except for the cognitive domain of reasoning. This variation was consistent with the findings of a recent systematic review on this topic that identified 46 studies addressing the issue of cognition and treatment response⁶. The review noted a high degree of variability between studies in testing measures, population, and outcomes. Despite this variability in outcomes, cognitive impairments of various kinds are prevalent in populations with substance use disorders and a significant number of studies have found aspects of cognitive functioning are associated with treatment outcome. Further research focused on optimizing interventions for patients with substance use disorder and cognitive impairments therefore seem warranted.

Strength of the current study includes the large sample size, real world clinical settings, and inclusion of patients with a variety of primary substance use disorders. An important strength for this study was that screening occurred in community settings and without stringent eligibility criteria, suggesting a representative sample of the treatment community.

Despite these strengths, several limitations should be noted. First, the study used a shorter version of the Microcog assessment, and global scores of cognition could not be calculated.

Second, this was an exploratory study, therefore corrections for multiple statistical tests were not utilized, which can increase the possibility of Type I error. This limitation is attenuated given lack of significant findings of moderation across both total and proficiency scores. The significant association between impairment in some neurocognitive domains and decreased retention should be interpreted with caution because of the multiple tests performed. Finally, the parent study was not specifically powered to detect an interaction between cognitive functioning and abstinence or retention outcomes. The absence of positive interaction might therefore have been due to lack of sufficient power.

In sum, it appears that an internet-delivered cognitive behavioral intervention for substance use disorders, the Therapeutic Education Systems, is equally effective across a spectrum of cognitive functioning among diverse patients seeking outpatient substance use treatment. Further study is needed to determine mechanisms by which cognitive functioning influences retention in treatment and to optimize technology-based interventions for those with cognitive impairment.

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Table 1.**Baseline Demographic and Clinical Characteristics**

	Treatment as Usual (TAU) N=252	Therapeutic Education System (TES) N=255
	n (%) or Mean (SD)	
Age (years)	34.2 (11.1)	35.6 (10.7)
Female	101 (40.1)	91 (35.7)
Race		
White	148 (58.7)	136 (53.3)
Black/African American	47 (18.7)	69 (27.1)
American Indian or Alaska Native	1 (0.4)	2 (0.8)
Asian	7 (2.8)	6 (2.4)
Native Hawaiian/Pacific Islander	5 (2.0)	7 (2.7)
Multi-racial	31 (12.3)	23 (9.0)
Other	13 (5.2)	13 (3.9)
Hispanic/Latino	29 (11.5)	26 (10.2)
Education		
< High School	58 (23.0)	60 (23.5)
High School/GED	149 (59.1)	161 (63.1)
> High School	45 (17.9)	34 (13.3)
Self-reported Primary Substance		
Alcohol	46 (18.3)	58 (22.7)
Cocaine	49 (19.4)	53 (20.8)
Other Stimulants	36 (14.3)	33 (12.9)
Opiates	60 (23.8)	54 (21.2)
Marijuana	59 (23.4)	49 (19.2)
Other	2 (0.8)	8 (3.1)
Cognitive Subtest Total Scores (M (SD), % Impaired)		
Attention and Mental Control		
Numbers Forward	8.5 (2.4), 18.3%	8.7 (2.7), 20.0%
Numbers Reversed	8.1 (2.6), 25.4%	8.2 (2.7), 27.5%
Wordlist 1	7.9 (4.5), 34.3%	7.1 (4.5), 41.2%
Wordlist 2	9.7 (3.1), 12.7%	9.6 (3.3), 13.7%
Reasoning		
Analogies	6.7 (2.8), 49.2%	6.7 (3.0), 49.8%
Object Match A	8.2 (4.0), 20.8%	8.4 (3.8), 17.4%
Object Match B	8.8 (2.9), 25.7%	8.4 (3.3), 33.2%
Spatial processing		
Clocks	11.0 (1.9), 3.2%	11.0 (1.8), 2.7%
Cognitive Subtest Proficiency Scores (M (SD), % impaired)		
Attention and Mental Control		

	Treatment as Usual (TAU) N=252	Therapeutic Education System (TES) N=255
	n (%) or Mean (SD)	
Numbers Forward	8.4 (2.3), 20.6%	8.5 (2.4), 22.4%
Numbers Reversed	7.6 (2.2), 29.4%	7.5 (2.1), 28.6%
Reasoning		
Analogies	7.9 (2.2), 25.4%	7.7 (2.4), 34.9%
Object Match A	8.5 (2.9), 24.8%	8.5 (3.0), 23.7%
Object Match B	9.4 (3.2), 17.3%	8.9 (3.5), 27.3%
Spatial processing		
Clocks	9.7 (1.3), 2.0%	9.7 (1.3), 1.2%

Table 2:

Interaction effects between Baseline cognitive scores (continuous) and treatment on Retention and Abstinence (N=507)

Cognitive Subtests	Retention	Abstinence
	F, p-value	
Total		
Attention and Mental Control		
Numbers Forward	F(1, 493)=0.68, <i>P</i> =.4092	F(1, 493)=1.51, <i>P</i> =.2202
Numbers Reversed	F(1, 493)=0.54, <i>P</i> =.4626	F(1, 493)=0.31, <i>P</i> =.5767
Wordlist 1	F(1, 492)=0.49, <i>P</i> =.4835	F(1, 492)=0.80, <i>P</i> =.3714
Wordlist 2	F(1, 492)=0.02, <i>P</i> =.8787	F(1, 492)=0.10, <i>P</i> =.7525
Reasoning		
Analogies	F(1, 493)=0.06, <i>P</i> =.8019	F(1, 493)=0.68, <i>P</i> =.4091
Object Match A	F(1, 489)=0.02, <i>P</i> =.8838	F(1, 489)=0.89, <i>P</i> =.3451
Object Match B	F(1, 488)=1.13, <i>P</i> =.2878	F(1, 488)=0.16, <i>P</i> =.6881
Spatial processing		
Clocks	F(1, 493)=0.59, <i>P</i> =.4442	F(1, 493)=3.61, <i>P</i> =.0579
Proficiency		
Attention and Mental Control		
Numbers Forward	F(1, 493)=0.00, <i>P</i> =.9870	F(1, 493)=0.01, <i>P</i> =.9093
Numbers Reversed	F(1, 493)=1.91, <i>P</i> =.1674	F(1, 493)=0.03, <i>P</i> =.8691
Reasoning		
Analogies	F(1, 493)=0.22, <i>P</i> =.6407	F(1, 493)=0.56, <i>P</i> =.4563
Object Match A	F(1, 489)=1.44, <i>P</i> =.2301	F(1, 498)=0.45, <i>P</i> =.5008
Object Match B	F(1, 488)=0.07, <i>P</i> =.7941	F(1, 488)=1.19, <i>P</i> =.2756
Spatial processing		
Clocks	F(1, 493)=0.32, <i>P</i> =.5700	F(1, 493)=0.02, <i>P</i> =.8961

Table 3:

Models of each Cognitive Subtest as a Main Effect adjusted by baseline abstinence on Retention and abstinence (N=507)

Cognitive Subtests	Retention	Abstinence
	Odds Ratio (95%CI), p-value	
Total Score		
Attention and Mental Control		
Numbers Forward	1.02 (0.95–1.10), <i>P</i> =.5257	0.98 (0.90–1.06), <i>P</i> =.5942
Numbers Reversed	0.99 (0.92–1.06), <i>P</i> =.7524	0.96 (0.88–1.04), <i>P</i> =.3055
Wordlist 1	1.01 (0.97–1.05), <i>P</i> =.7299	0.99 (0.94–1.04), <i>P</i> =.6347
Wordlist 2	0.98 (0.93–1.04), <i>P</i> =.4996	0.95 (0.89–1.02), <i>P</i> =.1273
Reasoning		
Analogies	1.09 (1.02–1.17), <i>P</i> =.0081	1.03 (0.95–1.11), <i>P</i> =.4820
Object Match A	1.06 (1.01–1.11), <i>P</i> =.0231	1.05 (0.99–1.11), <i>P</i> =.0882
Object Match B	1.07 (1.01–1.14), <i>P</i> =.0197	0.99 (0.92–1.06), <i>P</i> =.7249
Spatial processing		
Clocks	1.04 (0.94–1.15), <i>P</i> =0.4694	1.02 (0.90–1.14), <i>P</i> =.8070
Proficiency Score		
Attention and Mental Control		
Numbers Forward	1.04 (0.96–1.12), <i>P</i> =.3353	1.01 (0.93–1.11), <i>P</i> =.7789
Numbers Reversed	0.97 (0.89–1.06), <i>P</i> =.4943	1.02 (0.92–1.13), <i>P</i> =.6697
Reasoning		
Analogies	1.11 (1.03–1.21), <i>P</i> =.0108	1.05 (0.95–1.16), <i>P</i> =.3176
Object Match A	1.05 (0.98–1.11), <i>P</i> =.1706	1.06 (0.99–1.15), <i>P</i> =.1145
Object Match B	1.04 (0.99–1.10), <i>P</i> =.1405	1.01 (0.95–1.08), <i>P</i> =.7180
Spatial processing		
Clocks	1.04 (0.91–1.20), <i>P</i> =.5548	1.14 (0.96–1.35), <i>P</i> =.1467