PROJECT DESCRIPTION

February 7, 2018

1. Principal Investigator: Morris Bell, Ph.D.

2. Project Title: Cognitive Training in the Treatment of Alcohol Use Disorders in Older Veterans

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3. Purpose: This study aims to determine whether a combined intervention of cognitive remediation therapy (CRT) and Individual Drug Counseling (IDC) can benefit older Veterans in the initial phase of alcohol abuse treatment by improving abstinence outcomes and neurocognition. Substantial cognitive impairment is associated with alcohol use disorders (AUD),[7] and becomes worse with years of use and the aging processes[8-10]. In particular, Veterans entering treatment for AUD display cognitive deficits that may reduce their ability to benefit from treatment. While there is considerable variety in the severity and types of cognitive impairment found in newly recovering patients, problems with attention, learning and memory and executive function are common[8,21]. Since treatment requires that the individual be able to sustain attention, remember what is learned, and apply it to recovery, impaired underlying cognitive processes make successful treatment less likely. Moreover, problems with executive functioning and other pre-frontal cognitive processes have been associated with decreased treatment retention and poorer AUD treatment outcomes[7-9]. Although cognition can improve with sustained abstinence[27] it is during the early phase of recovery, when cognition is most impaired, that patients receive the most intensive treatment. AUD is a major cause of suffering and functional disability for older Veterans and a common co-morbidity with other physical and mental disorders. Finding more effective treatments of AUD remains a priority for VA healthcare.

The purpose of the proposed study is to learn whether CRT plus IDC, an evidence-based outpatient AUD treatment[56] is more effective than a Game-Play Placebo plus IDC. Game-Play Placebo has been used to provide equipoise between conditions in other CRT studies and in a current CRT study with mTBI Veterans funded by DoD being conducted by the PI. The proposed randomized controlled trial (RCT) will allow us to fulfill the following aims and test their related hypotheses:

Specific Primary Aim # 1: To determine if CRT+IDC is more effective than Game-Play Placebo +IDC in decreasing alcohol use in older Veterans during the 3 month active intervention period.

Ho1: CRT+IDC will be more effective than Game-Play Placebo+IDC in reducing heavy drinking days and decreasing days of use as measured by Breathalyzer and Timeline Follow-back Method (TLFB) during the 90 days of active intervention.

Secondary Aim #1: To determine if CRT+IDC is more effective than Game-Play Placebo+ IDC in sustaining decreased alcohol use in older Veterans at the end of 6 months (3 months after the active intervention period).

Ho2: CRT+IDC will be more effective than Game-Play Placebo+IDC in reducing heavy drinking days and decreasing days of use as measured by Breathalyzer and Timeline Follow-back Method (TLFB) for the 30 days preceding 6 month follow-up.

Secondary Aim #2: To determine if the combination of CRT and IDC is more effective than game play placebo and IDC in improving neurocognitive functioning.

Ho3: Veterans receiving CRT+IDC will show greater improvement than Veterans receiving Game-Play Placebo+IDC at 3 month follow-up on a global index of neurocognitive function, and on an index of working memory and an index of executive function.

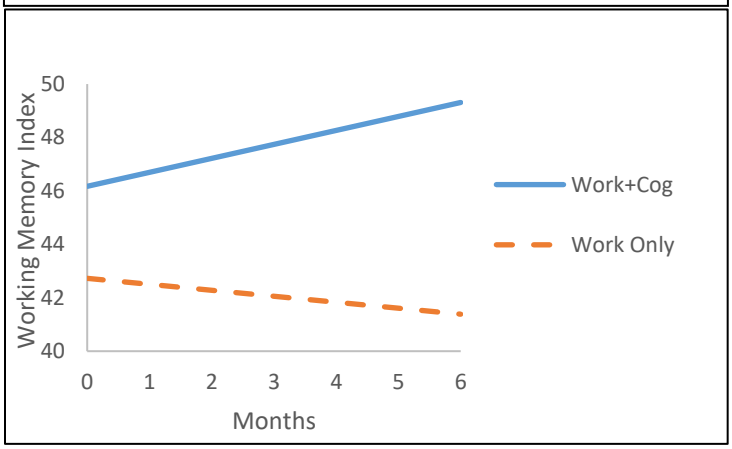
Ho4: Differential improvements in neurocognitive function will be sustained at 6 month follow-up

4. Background: Alcohol Use Disorders (AUDs) have a significant public health impact, cost billions of dollars in the US each year for treatment and lost productivity, and are highly prevalent in Veterans.[1-4] Estimated point prevalence is 5.5% in returning Veterans, higher than the 3.8% civilian estimate.[3] Lifetime prevalence for Vietnam Era Veterans was much higher when examined approximately 15 years after the end of the war, at almost 40% in men[4] as compared to male civilians at 30%.[2] Psychosocial behavioral interventions have some efficacy, but as revealed in a large VA cooperative multi-site study of a pharmacological augmentation (naltrexone), a high proportion in all arms of the study relapsed within one year.[5] A recently published study of the relative efficacy of mindfulness-based relapse prevention[6] in a civilian sample reported that 19% in the treatment as usual condition had returned to heavy drinking within 3 months. AUD is a major cause of suffering and functional disability for Veterans and a common co-morbidity with other physical and mental disorders. There is, therefore, a critical need to explore ways to improve treatment for AUDs in Veterans.

One possible avenue for improving AUD treatment outcomes may be to address neurocognitive impairments especially common in the early phase of recovery but often persisting over years[7] that interfere with the acquisition of new learning (e.g. attention and memory) and with better decision making (executive functioning). Indeed, alcohol related brain defects and associated cognitive impairments may contribute to the progression of AUD by affecting the individual's ability to benefit from treatment[8] and by impairing their daily community functioning, which in turn increases stress and subsequent relapse.[9,10] Recent research has suggested that cognitive remediation therapy (CRT) may improve attention, memory and executive function in schizophrenia and related disorders,[11-15] and there is evidence that these improvements are in turn associated with better skill acquisition in structured groups.[16] Many AUD treatments also require skill acquisition such as learning new ways of coping with craving, learning better methods for tolerating distress, being able to integrate feedback, and finding more constructive problem-solving strategies; therefore, improving attention, working memory and executive functioning could allow patients to get more out of these treatments.

There is a small amount of research to suggest that a CRT intervention could improve neurocognition for patients with substance abuse disorders (SUDs). In a landmark study, CRT was integrated into the context of a residential treatment[17, 18] and patients receiving CRT had better SUD outcomes. However, it is a major limitation of that research that the CRT was administered in the context of long-term residential treatment settings.[19] The only other published study of CRT for AUD also found significant improvement in neurocognition, well-being and compulsive craving, but it was within the context of an inpatient treatment unit.[20] These residential and inpatient studies provided CRT in a context that ensured that participation in the interventions could be tightly controlled and monitored. There were also other non-specific but stimulating activities such as a work-focused daily routine in the residential treatment that may have combined synergistically with the cognitive treatment. Although promising, these findings provide only limited support for CRT as a possible augmentation to SUD treatment and may not generalize to outpatient treatments. Nevertheless, the National Institute on Drug Abuse (NIDA) was sufficiently encouraged by these findings as well as the large neuroscience literature on the effects of SUD's on cognition to issue an RFA entitled "Cognitive Remediation Approaches to Improve Drug Abuse Treatment Outcomes (R21)". Our group (PI: Bell) was awarded an R21 pilot grant under this mechanism to demonstrate feasibility of CRT for outpatients with SUDs and to determine effect sizes on neurocognitive and substance abuse outcomes.

Figure 1. Work+Cog Working Memory increases over time.



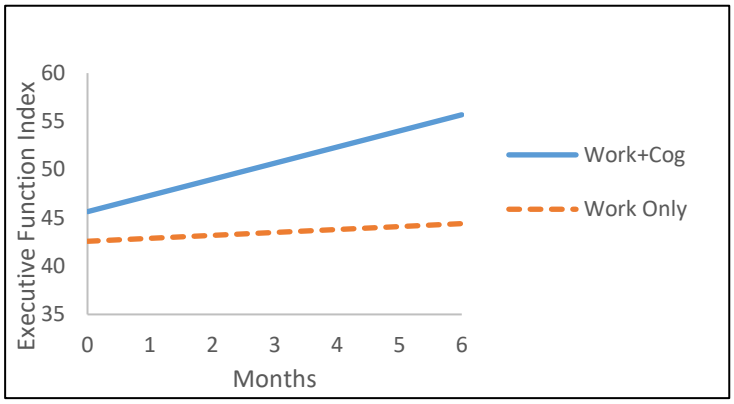
Note Simple slopes analyses of rates of change found Working Memory slope for Work+Cog was statistically significant (γ = .785, *se*=.314, *p* = .01). Slope for Work Only was not statistically different from zero (γ = -.335, *se*=.398, *p* = .264). Difference between groups' baseline scores was not statistically significant (γ = 3.445, *se*=2.627, *p* = .196). TimeXCondition is statistically significant (F = 6.7, p< .01)

In this NIDA funded study, CRT was combined with Work Therapy (CRT+WT) and compared with WT alone (Cognitive Training and Work Therapy in the Initial Phase of Substance Abuse Treatment; PI: Bell). Eighty-seven Veterans from substance abuse outpatient services were screened for eligibility within their first 30 days of sobriety; 48 were administered baseline assessments and randomized on a 1:1 ratio into CRT+WT (n= 24) or WT only (n = 24). They were on average 50.2 years of age, 49.4% Caucasian and most had felony convictions (80.5%). Twenty-eight had Alcohol Use Disorder (AUD) and 20 had other SUDs (amphetamine, cocaine, opiates). Our analysis of baseline neurocognitive assessments revealed high baseline rates of cognitive impairment, with 87.5% showing a clinically meaningful decline (1 SD) from a measure of their pre-morbid IQ on at least one cognitive measure. Moreover, 77.1% showed decline on 2 measures or more and the median was 3 measures out of 14 possible measures showing such a decline. Interestingly the highest rates of significant cognitive decline and impairment were on measures of verbal (50%) and non-verbal (45.8%) learning and memory with measures of executive function (41.7%) and working memory (37.5%) commonly

deteriorated. These findings add justification to focusing our cognitive training on processes that support learning, memory and executive function, cognitive functions required to benefit from recovery-oriented treatment and to remain abstinent.[27,28]

There were also differences noted in the R21 between those with a primary diagnosis of AUD (n = 28) and other SUDs (n = 20) with greater frequency of learning, memory and executive function decline and impairment in alcohol dependent participants and greater frequency of impairment in attention and response inhibition for participants with other SUDs. These group differences on performance measures were also mirrored in a self-report measure, the Barratt Impulsivity Scale, with other SUD participants scoring more than one standard deviation higher scores (more impaired) than AUD participants on Attention and Non-planning subscales. These findings indicate that these two groups differ in type of cognitive impairment and is a primary reason that we have decided to focus on Veterans with AUD for the proposed submission.

Figure 2. Work+Cog Executive Functioning increases over time.



Note Simple slopes analyses of rates of change found Executive Function slope for Work+Cog was statistically significant (γ = 2.509, *se*=.677, *p* = .001). Slope for Work Only was not statistically different from zero (γ = .457, *se*=.930, *p* = .478). Difference between groups' baseline scores was not statistically significant (γ = 3.067, *se*=2.263, *p* = .183). TimeXCondition is statistically significant (F = 4.87, p< .03)

We got excellent participation. Those randomized to the CRT+WT condition had an average of 213 hours of productive activity, performed an average of 39.6 (median =42.8) hours of cognitive training and attended on average 10.4 (median = 12) out of 13 weekly groups. The WT Only group had similar total hours of productivity and group attendance. Follow-up rates were also very good, with 44 out of 48 (95.7%) completing 3 months follow-up and 42 out of 48 (87.5%) completing 6 month follow-up. Thus, this pilot demonstrated excellent adherence and study retention, well above what is usually found in SUD research.

Neurocognitive outcomes were analyzed by creating 5 composite indices: Visual and Verbal Working Memory, Visual and Verbal Learning, Processing Speed, Attention, and Executive Function. Mixed effects model for 3 points in time (Baseline, 3 month and 6 month follow-up) revealed significant Time effects on all indices and significant differences (TimeXCondition) favoring CRT+WT on the Visual and Verbal Working Memory Index ($p < .01$; ES Cohen's d = .84) and on the Executive Function Index ($p < .05$; ES Cohen's d = .72). All index trends favored the CRT+WT condition, and a Global Index Composite Score showed a non-significant trend with an Effect Size of Cohen's d = .36.

Subanalyses that examined differential responses to treatment by primary diagnosis (AUD or Other Substances) found generally greater gains across indeces for those with AUD. For example, Verbal Learning (HVLT scores) slopes across the 3 learning trials at baseline and at 3 month follow-up were compared for the two diagnostic groups by condition. AUD participants showed significant improvement ($p < .01$) whereas the change in slope was not significant for those with other SUDs. These improvements in HVLT were sustained at 6 month follow-up. Moreover, the Global Index Composite Score for AUD participants showed a near-significant trend ($p < .07$) with an Effect Size of Cohen's d = .71, almost double the effect size of d = .36 when all participants were included.

Regarding SUD outcomes, CRT+WT had a mean of 87.3/90 (97%) days of abstinence (PDA) in the first 90 days, and 28.2 days of abstinence in the 30 days (94%) prior to 6 month follow-up. They also averaged 23.8/26 (91.5%) weeks of abstinence out of 26 weeks. However, the WT only condition produced similarly impressive SUD outcomes, so there was no differences by condition at either 3 month or 6 month follow-up.

Results of the R21 study suggest that cognitive training is acceptable to older Veterans with SUD in outpatient treatment and leads to significant improvements in cognitive functioning beyond that of normal recovery with medium to large effect sizes. Moreover AUD participants may have benefited more from

CRT+WT than those with other SUDs. In particular, CRT led to recovery of verbal learning for Veterans with AUD, a crucial cognitive ability for IDC, which depends upon verbal learning to be effective.

5. Significance: Alcohol Use Disorders (AUDs) have a significant public health impact and are highly prevalent in Veterans. Alcohol related brain effects on neurocognition (attention, memory and executive function) reduce ability to benefit from current treatments. These cognitive impairments are especially common in the early phase of recovery, persist over years and get worse with age. Recent research suggests that cognitive remediation therapy (CRT) may improve attention, memory and executive function in other disorders, and our just completed pilot study with AUD Veterans found significantly greater improvements for those receiving CRT. This study will be the first to examine AUD outcomes and neurocognitive improvements when CRT is combined with a standardized alcohol treatment for outpatients with AUD. Findings will determine whether CRT augmentation can benefit Veterans with AUDs.

6. Research Plan:

Design: This is a double-blind, intent-to-treat randomized controlled trial (RCT) that will randomize 90 Veterans with a current and primary DSM-V (APA, 2013) alcohol use disorder (AUD) into two conditions. Participants will be within the first 30 days of recovery when consented, and those who meet all inclusion and exclusion criteria will be randomly assigned (ratio 1:1) to CRT+IDC or Game-Play Placebo+IDC for 13 weeks of active intervention. All participants will continue to receive their usual alcohol abuse outpatient treatment. Psychotropic medications are sometimes prescribed and will be tracked in this study. Primary outcome is days of use and number of heavy drinking days (4 or more standard drinks per occasion for women and 5 or more for men; NIAAA website). Secondary neurocognitive and community function outcome measures are listed below in "Measures" section. Treatment adherence will be assessed. Assessments will be performed at baseline, 7 weeks, 13 weeks (end of active intervention) and 26 weeks.

Participants: We expect to recruit by clinical referral and by flyer postings in clinical settings approximately 150 individuals of whom about 110 will pass the phone screening. Following informed consent procedures, these 110 will complete all baseline assessments and we expect that 90 participants will meet criteria for a primary alcohol use disorder and all other inclusion and exclusion criteria. Participants will be recruited from the VACHS substance abuse program. All study participants will be part of Dr. Joanna Fiszdon's subject re-contact repository (#0009).

Inclusion criteria: Males and females at least 21 years of age; fluency in English and a 6th grade or higher reading level; meets DSM-V criteria for a current Alcohol Use Disorder; referred for the study within 30 days of detoxification or last substance use according to medical records; willingness to attend follow-up assessments at 13 weeks and 26 weeks; willingness to submit to Breathalyzer screenings and Urine Toxicology screenings.

Exclusion criteria: Lifetime diagnosis of a psychotic disorder, not induced by drug use; current prescribed treatment of opioids or benzodiazepines, which may affect new learning; involvement in a legal case that may lead to incarceration during study period; residential plans that would interfere with participation; medical illness that may significantly compromise cognition (e.g. Parkinson's, Alzheimer's, Huntington's Chorea, Moderate or greater TBI); an uncorrected sensory impairment (hearing or sight) that would seriously interfere with cognitive training; pre-morbid IQ estimate below 70; unstable housing or lack of commitment to staying within a geographic area that would make follow-up possible*)*; unwillingness to provide contact information of someone who can help us contact the participant in the event that we are unable to maintain contact directly. They must be competent to give written informed consent and HIPAA authorization.

Measures: Primary outcome measures are Heavy Drinking Days and Days of Use for the 90 days of active intervention as measured by Time-Line Follow-back (TLFB) Alcohol Use Assessments. This assessment asks for days of use and how many drinks and what types of drinks were consumed at each occasion during the preceding week. Other drug use is also recorded. TFLB assessment is done weekly along with an alcohol urine toxicology test and a Breathalyzer test. If more than one week has passed since the last TFLB assessment, the TLFB procedure is used to review the entire lapsed period. For example, if it has been 14 days since the last TLFB, then going backwards, the interviewer would ask about alcohol use for those 14 days. Breathalyzer testing and an alcohol urine toxicology test is always performed first, followed by the TFLB. This sequence encourages disclosure even though Breathalyzer results only reflect alcohol use during the past day. The alcohol urine toxicology test reflects a window of up to 80 hours of prior use. A positive Breathalyzer test and an alcohol urine toxicology test is regarded as definitive evidence of alcohol use and has precedence over self-report when the person denies use. However a negative Breathalyzer test or a negative alcohol urine

toxicology test is not regarded as evidence of abstinence when the person states that he/she used alcohol. Secondary outcomes include Heavy Drinking Days and Days of Use for the 30 days preceding 6 month follow-up using Breathalyzer and the Time-Line Follow-back procedure.. Changes in Alcohol Craving from baseline at 3 and 6 month follow-up will be examined. Neurocognitive outcomes at 7 weeks and at 3 month and 6 month follow-ups are also secondary outcomes. Measures are presented in the following chart by category. They include AUD related assessments and cognitive assessments by domain. These domains include attention, working memory, learning and memory, executive function, and processing speed. We also include measures of risk taking and impulsivity because they are strongly associated with AUD and may be inhibited by improved executive functions. A treatment utilization form is included as a weekly measure of treatments received beyond study procedures. Given space limitations, descriptions are not provided, but references are included. From our experience in the R21, which used very similar assessments, Baseline is estimated to be 3-4 hours and follow-up evaluations are 2-3 hours. Inter-rater agreements were in the good to excellent range in prior studies and in the R21, and agreement drift is checked through consensus meetings.

Instrument	Source	Blinded	Baseline	Weekly	7wks	13wks	26wks
Inclusion/Exclusion	Chart + Interview						
Demographics & M.I.N.I[39]	Interview		X				
AUD Related Assessments							
EtG Urine Tox Screen			X	X		X	X
Alcohol Breathalyzer		X	X	X		X	X
Time-Line Follow-back Alcohol Use Calendar[40]	Interview	X	X	X		X	X
Addiction Severity Index modified[41]	Interview	X	X			X	X
Drug Urine Tox Screen			X			X	X
Penn Alcohol Craving Scale[42]	Self		X	X		X	X
Premorbid-IQ Estimate							
Wechsler Test of Adult Reading (WTAR)[43]	Perform	X	X				
Attention							
Integrated Visual & Auditory Continuous Performance Test-2[44]	Perform	X	X		X	X	X
Trails A & B[45]	Perform	X	X		X	X	X
Working Memory							
Digit Span[46]	Perform	X	X		X	X	X
Spatial Span[47]		X	X		X	X	X
Learning and Memory							
Hopkins Verbal Learning Test (multiple forms)[48]	Perform	X	X		X	X	X
Logical Memory I + II[47]	Perform	X	X		X	X	X
Brief Visual Motor Test[49]	Perform	X	X		X	X	X
Babcock Story Recall Test [59]	Perform	X	X		X	X	X
Executive Function							
Wisconsin Card Sort Test (64 cards)[50]	Perform	X	X		X	X	X
D-KEFS Tower Test[60]	Perform	X	X		X	X	X
D-KEFS Color-Word Interference Test[61]	Perform	X	X		X	X	X
Mazes[51]	Perform	X	X		X	X	X
Processing Speed							
Digit Coding[46]	Perform	X	X		X	X	X
Symbol Search[46]	Perform	X	X		X	X	X
Self Assessments							
Barrett Impulsivity Scale[52]	Self		X				
Beck Depression Inventory[62]	Self		X			X	X
Beck Anxiety Inventory[63]	Self		X			X	X
VR-12[64]	Self		X			X	X
Bell Object Relations &	Self		X				

Reality Testing Inventory[65]							
WHODAS 36 Item Self Report[66]	Self		X			X	X
Patients Assessment of Own Functioning Inventory (PAOFI) [67]	Self		X			X	X
Treatment Utilization							
Treatment Utilization Form	Chart+ Interview		X	X	X	X	X

Procedures:

Informed Consent and HIPAA authorization will be obtained according to procedures approved by the VACHS IRB. A certificate of confidentiality will be requested.

Randomization: Participants will be randomized into CRT+IDC or Game-Play Placebo+IDC conditions. Randomization will be stratified by neurocognitive deterioration (Yes/No) based on having 3 or more baseline cognitive measures greater than 1 SD below premorbid estimate (3 was the median number of measures below expected value in the pilot R21 study described above). Variable block randomization tables will be created based on computer generated blocks using random permuted blocks of 2 to 6 by our statistician from Yale Center for Analytic Science. Sealed envelopes containing the randomization by participant entry number will be created and opened when a participant's pre-randomization procedures are completed.

Assessments Procedures: Measures are listed in the table above. Preliminary screening will be performed with a brief interview usually by phone that describes the inclusion and exclusion criteria in simple language and asks if the individual believes he/she meets criteria. After informed consent, participants will undergo DSM-V diagnostic procedure with the M.I.N.I diagnostic interview adapted to DSM-V.[39], the WTAR to determine reading level and pre-morbid IQ estimate and a thorough demographic and psychosocial interview to determine whether they are eligible for the study according to inclusion and exclusion criteria. Information from medical records and referring clinicians are also used. During the active intervention participants will have weekly Breathalyzer tests and a weekly TLFB Alcohol Use Calendar. Critical events will also be recorded along with on-going process data about participation in procedures and response to cognitive training. Treatment utilization will be tracked weekly and at follow-ups by chart review and interview. Baseline assessments will be repeated at 3 months and 6 months. A briefer battery of cognitive tests will be performed at 7 weeks. The participant time line is shown in the table below:

Participant Time-Line

Week	Procedure
-1	Screening to determine eligibility and Informed Consent
0	Baseline Assessment, and Randomization
1-13	Intervention Condition with Weekly Alcohol Use Assessments & Breathalyzer & Alcohol Urine Toxicology Screen
7	Cognitive Assessment
13	Complete Intervention Condition and Follow-up 1 Assessment
26	Complete Follow-up 2 Assessment

Blinding: This is possible because of our ability to have specialized staff for each purpose. Cognitive Remediation/ Individual Drug Counselors (IDCs) are required to be un-blinded in order to provide support for participants in their assigned conditions. They will be distinct from the psychometrician doing weekly and follow-up assessments. Blinded Roles: Staff responsible for the administration and scoring of participants' assessments after randomization will remain blinded to participant treatment condition. To prevent un-blinding, the following controls will occur: 1.The treatment condition (CRT+IDC) and the control condition (Game-Play Placebo+IDC) will be identified as "Cognitive Training A" and "Cognitive Training B"; 2. Participants will be reminded not to discuss details related to treatment with the psychometrician prior to the start or at the conclusion of their visit (a sign on the desk reminds the participant of this rule); 3. Research staff will be instructed not to discuss details of treatment related to either cognitive training arm during informed consent or at any other point throughout the study. The informed consent accurately describes this study as a comparison of two approaches to using challenging computer games to improve cognition. Every effort will be

made to avoid the implication that one condition is the experimental condition and the other is the control condition. 4. Accidental un-blinding of the psychometrician (e.g. through the un-intended viewing of treatment sessions) will be avoided. 5. Signs will be posted in appropriate areas reminding staff and participants not to discuss treatment details in open locations. 6. Mid-way and at the end of the trial, the psychometrician will be asked questions to evaluate the integrity of the blinding procedures employed throughout the trial. The psychometrician will complete a rating of degree of blindness (Definite CRT+IDC to Definite Game-Play Placebo+IDC) after each assessment. The primary outcome of Heavy Drinking Days and Days of Use is relatively immune to bias, particularly since it is informed by chart review and weekly Breathalyzer testing. All procedures are already in place and were successfully implemented in the R21.

Treatment Conditions

Individual Drug Counseling (IDC): Once randomized to condition, all participants meet individually each week with their Individual Drug Counselor, who follows the manualized IDC treatment. All participants receive these procedures during the 13 weeks of active intervention. IDC has been summarized in a published manual for study therapists[56]. It is based on the disease model of addiction. Clients are counseled regarding such fundamental concepts of AUD treatment as pointing out when a client is denying the extent and consequences of alcohol use, teaching clients to avoid "people, places and things," and encouraging clients to make a personal inventory of qualities to change. It is practical and behavioral, with a focus on abstinence in the here and now. The manual describes sessions devoted to treatment engagement, early abstinence and maintenance of abstinence. IDC does not prevent clients from getting the treatment-as-usual they have been getting prior to enrollment. In addition to standard IDC, several adaptations have been made to IDC for this study. These include a) research staff will make phone calls to remind participants of their appointments and to coordinate with other clinicians to schedule appointments; b) weekly appointments will be scheduled over 13 weeks, with rescheduling and drop-in appointments allowed; c) abstinence is presented as desirable but to prevent the Abstinence Violation Effect (a slip becoming a full-relapse), relapse prevention and harm reduction will be emphasized; and d) participants are encouraged to participate in available AUD treatment groups at VACHS, whereas classic IDC more specifically refers to Twelve Step groups.

CRT and Game-Play Placebo: This study employs two computerized programs for cognitive enhancement. The CRT+IDC condition uses BrainHQ and the Game-Play Placebo uses a set of ordinary computer games. Participants will be asked to use their assigned program for one hour per session, up to five sessions per week, over three months (maximum of 65 sessions). A particular advantage of this training is that after participants are trained in how to log on to the training website and are familiar with the training programs, they may continue their training on site at the Learning Based Recovery Center (LBRC)'s "Cog Lab" or at another quiet location of their choice. If the participant prefers, it is also possible to use the program on their own device at home, use a computer available at their residence or a computer at a local library. The program allows participants to change locations as fits their schedule. Usage and progress tracking for both programs is completely web-based, allowing participants to move between computers as is convenient for them. Research staff carefully monitor usage and progress each week and use that information in phone call counseling sessions regardless of condition assignment.

Also, while we will encourage participants to complete 5 sessions per week of training, we will also let them know that we understand that not every participant will be able to maintain this schedule. We will let them know that if they feel they need to drop to a lower number of sessions per week that they should discuss it with their research counselor who will work out a schedule that is feasible in their overall life circumstances. There are also circumstances in which the participant may wish to practice more than 5 sessions in a week, particularly when they missed some practice days in a previous week. This is allowable but should be discussed with the participant's research counselor. Participants may also choose to do their computer-based training even if they miss a weekly IDC appointment. The research counselor will contact the participant by phone to encourage continued participation and to learn about any alcohol or other substance use during the week. If a participant wishes to stop or minimize use of the training program, they will still be encouraged to continue their IDC sessions, and contact will be maintained by phone, if possible, even if the participant does not regularly come to IDC sessions. Potential reasons for discontinuing might include a change in work circumstances, a change in residence, health issues, family/personal issues, relapse or a lack of interest in program activities. However, the participant may want to meet their personal commitment to the basic scientific research of the study and will be encouraged to participate in follow-up assessments.

Brain HQ is a computerized cognitive remediation program consisting of a set of specific cognitive exercises and is commercially available on the internet. To disguise to which condition the participant is assigned, Posit Science created a special study log-in site so that a participant encounters the same initial screens when entering the system regardless of condition. This special study website was created for the DoD funded mTBI study (BRAVE) currently in progress, and Posit Science has agreed to allow us to use it for the this study. To use BrainHQ, a participant opens a standard web browser on a broadband connected computer and goes to the study website. The participant then logs into the website (using a study-provided screen name that contains no personally identifiable information). A game-like experience begins, where the participant is encouraged to earn points and in-game rewards to advance. To do so, the participant selects one of the cognitive exercises scheduled for the day, and performs that exercise for fifteen minutes. After each trial, the difficulty of the next trial is updated to ensure that within a session, the participant gets ~85% of trials correct. Summary screens including game metrics (points, levels) and exercise metrics (usage, progress) are shown to the participant at the end of each session. BrainHQ has multiple cognitive exercises. The scheduling mechanism ensures that the participant progresses through the exercises in a defined order, generally moving from simpler (early sensory processing) exercises to more complex (multimodal, cognitive control) exercises over the course of the three month experience. At any point in time, the participant only has access to a subset (typically six) of these exercises, four of which are performed per day. Each exercise has specific criteria for completion or plateaued performance, and after those criteria are met, the exercise is removed from the active set and the next exercise is added to the active set. This ensures ongoing novelty and engagement, while allowing for smooth progression through the complete set of exercises. The exercises include many of the auditory and visual tasks used in our R21 pilot study that address attention, working memory, processing speed, memory and learning, and executive function

Game-Play Placebo**:** The active control program is composed of 13 ordinary computer games. It is designed to 1) be a face-valid approach to cognitive remediation to maintain participant blind and match BrainHQ in any halo or expectation effect, 2) match BrainHQ in overall program use intensity, requirements for attention, delivered rewards, and overall engagement, and 3) provide a comparison group that matches BrainHQ with the exception of the specific scientific approach to cognitive remediation embodied by BrainHQ to allow the study results to be interpreted in light of that specific approach. The Game-Play Placebo is launched in the same manner as BrainHQ. The participant chooses from a number of ordinary computer games (e.g., hangman, boggle, word scramble, chess). The games are chosen for their face-validity in improving cognitive function. The number, availability, and time spent on each game is managed by the game controller to generally match the experience of progress through BrainHQ. Only games providing face-valid cognitive stimulation and that are rated E (for everyone) by the Entertainment Software Rating Board (ESRB) will be used. This is the same control condition currently in use in the DoD funded mTBI study (BRAVE).

Participant Compensation

To encourage participation, small incentives are included in this study to compensate for time and inconvenience. Participants will receive $50 for the interview and screening procedures, $25 for the 7 week assessment, $75 for 3 month follow-up, and $75 for 6 month follow-up, for a total of $225 for assessments. They will receive $10.00 for each individual session of Individual Drug Counseling plus $5.00 for the breathalyzer test during 13 weeks for a maximum total of $195.00. They will also receive $5 per hour for time spent doing cognitive training for a maximum total of $325 for 65 hours of training. The maximum total compensation for full participation in all procedures over 26 weeks is $745. Payment will be made according to current VA procedures. They may choose to have a check mailed to the address they provide or they may choose electronic fund transfer (EFT) if they provide required banking information or they may choose to receive gift certificates for use at the VCS canteen (retail store) or VCS cafeteria here at the VA

Concomitant Treatment and Staff Training

Approach to Concomitant Treatment: The aim of this study is to determine efficacy in an outpatient setting, and there will be wide variability in how much participants utilize concomitant treatment-as-usual. Concomitant treatment will be tracked using our Treatment Utilization form to determine whether CRT+IDC increases participation in concomitant treatment and if such an increase mediates its effect on AUD outcomes. All participants will have access to a VA primary treating clinician. Primary clinicians will coordinate the participant's access to other available treatments including a prescribing physician, restricted settings (inpatient, day hospital and detoxification), residential assistance (supervised housing, group homes, rent

assistance), outpatient substance abuse treatment, and vocational rehabilitation. Participants are encouraged to remain engaged in outpatient services and to do so throughout the study. Their study condition is meant to be an augmentation to their usual treatment at VACHS. Part of the consent process includes permission for research staff to speak with their clinician and to convey clinically relevant information at the discretion of the PI. Moreover, all participants will have at least monthly notes recorded in their electronic medical record relevant to clinically related events that may occur during research activities. This is carefully explained in the consent form and is for the medical welfare of the participant. These procedures are to ensure that participants experience the study intervention as an augmentation to their on-going AUD treatment.

Therapist Training to Conduct Individual Drug Counseling: Training will be overseen by Dr. Rosen and will employ multiple modalities: review of the therapy manual, role plays, and group meetings to discuss problematic aspects of the therapy. Digital recordings of IDC delivered as part of Dr. Rosen's RO1 are available from the NIAAA website. Hiring counselors who have an AUD treatment background is important because when experienced counselors deliver IDC, it is readily learned and delivered with fidelity[57, 58]. In the main clinical trial, IDC was the intervention rated as being delivered with the highest fidelity to the manual[59].

Therapist Supervision of IDC: The therapist will be supervised intensively by Dr. Rosen until the therapist understands IDC and delivers it effectively, as verified by review of therapy videotapes and therapy notes. Dr. Rosen will not be one of the independent raters of the videotapes for fidelity purposes and thus, will be able to review the videotapes in supervision without compromising the ratings' impartiality. After the initial period, supervision will be phased back to weekly, with as-needed consultation.

Assessment Training. The psychometrician is independent of the research counselors and is kept blind to condition. Our assessors have already been trained through our previous research. Dr. Bell monitors the procedures and carefully reviews assessment data weekly for any inconsistencies that may suggest errors in scoring or data entry. If new staff is added during the course of the proposed study, Dr. Bell takes responsibility for training them in these procedures by having them observe assessments, perform assessments under his supervision and by determining inter-rater agreement. In the proposed study, the only clinical assessments are MINI diagnosis at baseline, the Time Line Follow-back Alcohol Use Calendar, and the ASI.

Data Management, Sample Size Calculation, and Analysis Plan

Data management will follow procedures established in previous studies Our research team will use Teleforms® software to create, clean, and enter quantitative data. Forms are created with barcodes that are scanned using Teleforms' object character recognition software. Data is extracted and automatically inputted to an SPSS database. Filters flag data that needs to be re-checked by a person such as unclear characters, out-of-range variables and logical inconsistencies. The research assistant will scan files monthly so that errors can be readily corrected and consequential differences between treatment types (e.g., different levels of attrition) can be monitored closely. SPSS (vers. 21) will be used as the primary analysis software. Baseline characteristics will be tested for any significant differences between randomized conditions using parametric and non-parametric procedures as required by the nature of the data. Data reduction is a major issue in a relatively small N, large-number-of-variables study. We have chosen a primary outcome measure (Heavy Drinking Days and Days of Use in the first 90 days) to reduce Type I error. Heavy Drinking Days and Days of Use will be determined by Time-Line Follow-back calendar and Breathalyzer results. If a participant cannot provide more exact information about days of use for that week, then we will assume continuous use.

Neuropsychological data will be indexed into established domain scores (attention, working memory, memory and learning, executive function, processing speed) and a composite index score. The design is intent-to-treat. Distributions of continuous data will be tested for normality and transformed when necessary. Randomized conditions will be tested for potential differences on baseline values. We believe that our stratified randomization will make it unlikely that significant differences will be found; however, any significant differences will be used as covariates in between-group comparisons.

Sample size: We plan to screen approximately 150 Veterans and recruit 110 Veterans (after telephone screen) with a current and primary DSM-V AUD who are within the first 30 days of recovery and expect that 90 will be eligible for randomization after baseline testing. We expect better than a 90% retention rate at the 3 month time point, and thus expect to have more than 80 individuals for the primary analysis. Assuming equal loss-to-follow-up in each of the two treatment arms, we will have at least 40 individuals per group. Using data

from our pilot study and the study done by Bowen et al.,[6] we estimate mean Days of Alcohol Use in the Placebo + IDC arm to be 4 and the number of Heavy Drinking Days to be 3 at 90 days. Using PASS 12 (Kaysville, Utah) Poisson regression procedure, and assuming an over-dispersion parameter of 2 for days of use and 4 for heavy drinking days, we will be able to detect a 37% reduction in days of use and a 55% reduction in days of heavy drinking with 80% power and a type I error rate of 5% for each outcome in the CRT+IDC arm compared to the Game-Play Placebo + IDC arm. Stratification on neurocognitive functioning was not factored into the sample size calculations. In most situations, stratification will increase precision, and thus we will have a conservative estimate of the detectable effects. Given that we expect to lose another 5-10% of individuals to follow-up, we will have less power to detect the same effect size at 6 month time point.

Analysis Plan: We will use a Poisson regression model accounting for over-dispersion to compare the CRT+IDC arm to the Game-Play Placebo+IDC arm on the primary outcomes: Days of Use and Days of Heavy Drinking at 90 days (Ho1). We will use the same model to compare the CRT+IDC arm to the Game-Play Placebo+IDC for the 6 month time point, a secondary endpoint (Ho2). We will conduct sensitivity analysis using a negative binomial model and assess any differences in the results compared to the Poisson model with over-dispersion[60]. To evaluate neurocognitive functioning (global index; index of working memory; index of executive function, etc..), we will use generalized estimating equations and/or linear mixed models (if the data appear normally distributed) to account for the correlation between time points (baseline, 3 months, 6 months) for a given individual. We will test for a significant treatment arm by time interaction to determine whether the combination of CRT+IDC is more effective than Game-Play Placebo+IDC in improving neurocognitive outcomes (Ho3, Ho4). We use contrast statements to explore the individual time point effects. In all models, we will adjust for neurocognitive functioning (the stratification variable). We will use the Benjamini-Hochberg procedure[61] to control the false discovery rate for all secondary outcomes keeping the overall level of significance at 0.05. However, given the limited sample size in this study, we do not expect to reach statistical significance unless there are large effects, especially for the secondary outcomes, and thus plan to use these results as hypothesis generating for a larger confirmatory study.

References

1. Harwood H. Updating estimates of the economic consts of alcohol abuse in the United States: Estimates, updated methods, and data. Report prepared by the Lewin Group for the National Institute of Alcohol Abuse and Alcoholism. Edited by NIAAA. Rockville Maryland, NIAAA; 2000.
2. Hasin DS, Stinson FS, Ogburn E, Grant BF. Prevalence, correlates, disability and comorbidity of DSM-IV alcohol abuse and dependence in the Unisted States: results from the National Epidemiologic Survey on Alcohol and Related Conditons. *Arch Gen Psychiatry*. 2007;64:830-842.
3. Seal KH, Cohen G, Waldrop A, Cohen BE, Maguen S, Ren L. Substance use disorders in Iraq and Afgahan istan veterans in VA healtcare, 2001-2010: Implications for screening, diagnosis and treatment. *Drug Alcohol Depend*. 2011;116:93-101.
4. Kulka RA, Schlenger WE, Fairbank JA, Hough RL, Jordan BK, Marmar CR, Weiss DS. Trauma and the Vietnam war generation: Report of Findings from the national Vietnam Veterans Readjustment Study. Brunner/Mazel, New York, NY, 1990.
5. Krystal JH, Cramer JA, Krol WF, Kirk GF, Rosenheck RA. Naltraxone in the treatment of alcohol dependence. *N Engl J Med*. 2001;345:1734-1739.
6. Bowen S, Witkiewitz K, Clifasefi SL, Grow J, Chawla N, Hsu S, Carroll HA, Harrop E, Collins SE, Lustyk K, Larimer ME. Relative efficacy of mindfulness-based relapse prevention, standard relapse prevention, and treatment as usual for substance Use disorders: A randomized clinical trial. *JAMA Psychiatry.* 2014;71(5):547-556.
7. Bernardin F, Mahuet-Bosser A, Paille F. Cognitive impairments in alcohol-dependent subjects. *Frontiers of Psychiatry*. 2014;5:1-6.
8. Blume, A. W., Schmaling, K. B., & Marlatt, G. A. Memory, executive cognitive function, and readiness to change drinking behavior. *Addictive Behaviors.* 2005;30:301–314.
9. Blume, A. W., & Marlatt, G. A. The role of executive cognitive functions in changing substance use: What we know and what we need to know. *Annals of Behavioral Medicine.* 2009;37:117–125.
10. Bowden, S. C., Crews, F. T., Bates, M. E., Fals-Stewart, W., & Ambrose, M.L. Neurotoxicity and neurocognitive impairments with alcohol and drug-use disorders: Potential roles in addiction and recovery. *Alcoholism:Clinical and Experimental Research*. 2001;25:317–321.
11. Krabbendam L, Aleman A. Cognitive rehabilitation in schizophrenia: a quantitative analysis of controlled studies. *Psychopharmacology.* 2003;169(3-4):376-382.
12. Kurtz MM, Moberg PJ, Gur RC, Gur RE. Approaches to cognitive remediation of neuropsychological deficits in schizophrenia: a review and meta-analysis. *Neuropsychology Review.* 2001;11(4):197-210.
13. Anaya A, Aran, AM, Ayuso-Mateos, JL, Wykes T, Vieta E, Scott J. A systematic review of cognitive remediation for schizo-affective and affective disorders. *Journal of Affective Disorders.* 2012; 142(1-3):13-21.
14. Twamley EW, Jeste DV, Bellack AS, Twamley EW, Jeste DV, Bellack AS. A review of cognitive training in schizophrenia. *Schizophrenia Bulletin.* 2003; 29(2):359-382.
15. McGurk SR, Twamley EW, Sitzer DI, McHugo GJ, Mueser KT. A meta-analysis of cognitive remediation in schizophrenia. *American Journal of Psychiatry.* 2007;164(12):1791-1802.
16. Silverstein SM, Spaulding WD, Menditto AA, et al. Attention shaping: A reward-based learning method to enhance skills training outcomes in schizophrenia. *Schizophrenia Bulletin.* 2009;35(1):222-232.
17. Fals-Stewart W, Lam WK. Computer-assisted cognitive rehabilitation for the treatment of patients with substance use disorders: a randomized clinical trial. *Experimental & Clinical Psychopharmacology.* 2010;18(1):87-98.
18. Grohman K, Fals-Stewart W. Computer-assisted cognitive rehabilitation with substance-abusing patients: effects on treatment response. *Journal of Cognitive Rehabilitation.* 2003; 21:2-9.
19. Fals-Stewart W, Schafer J. The relationship between length of stay in drug-free therapeutic communities and neurocognitive functioning. *Journal of Clinical Psychology.* 1992;48:539-543.
20. Rupp CI, Kemmler G, Kurz M, Hinterhuber H, Fleischhacker WW. Cognitive remediation therapy during treatment for alcohol dependence. *J Stud Alcohol Drugs*. 2012;73:625-634.
21. Richardson-Vejlgaard R, Dawes S, Heaton RK, Bell MD. Validity of cognitive complaints in substance-abusing patients and non-clinical controls: the Patient's Assessment of Own Functioning Inventory (PAOFI). *Psychiatry Research.* 2009;169(1):70-74.

22. Wexler BE, Bell MD. Cognitive remediation and vocational rehabilitation for schizophrenia. *Schizophrenia Bulletin.* 2005;31(4):931-941.
23. Bell MD, Fiszdon J, Bryson G, Wexler BE. Effects of Neurocognitive Enhancement Therapy in schizophrenia: normalization of memory performance. *Cognitive Neuropsychiatry.* 2004;9(3):199-211.
24. Bell MD, Bryson GJ, Greig TC, Fiszdon JM, Wexler BE. Neurocognitive enhancement therapy with work therapy: Productivity outcomes at 6- and 12-month follow-ups. *Journal of Rehabilitation Research & Development.* 2005;42(6):829-838.
25. Bell MD, Fiszdon JM, Greig TC, Wexler BE, Bryson G. Neurocognitive enhancement therapy with work therapy in schizophrenia: a six month follow-up of neuropsychological performance. *Journal of Rehabilitation Research & Development.* 2007;44(5):761-770.
26. Bell MD, Zito W, Greig T, Wexler BE. Neurocognitive enhancement therapy with vocational services: work outcomes at two-year follow-up. *Schizophrenia Research.* 2008;105(1-3):18-29.
27. Teichner G, HornerMD, Roitzsch JC, Herron J, Thevos A. Substance abuse treatment outcomes for cognitively imparied and intact outpatients. *Addictive Behaviors.* 2002;27:751-763.
28. Wolwer W, Burtscheidt W, Redner C, Schwartz R, Gaebel W. Out-patient behaviour therapy in alcoholism:Impact of personality disorders and cognitive impairments. *Acta Psychiatric Scandinavica*. 2001;103:30-37.
29. Goldman-Rakic PS. Architecture of the prefrontal cortex and central executive. *Annual NY Academy of Science*. 1995; 769:71-83.
30. Goldman-Rakic PS. Regional and cellular fractionation of working memory. *Proc Natl Academy Science*. 1996; 93:13473-13480.
31. Arnstein Af, Li BM. Neurobiology of executive functions: catecholamine influences on prefrontal cortical functions. *Biological Psychiatry*. 2005; 57:1377-1384.
32. McClure SM, Ericson, KM, Laibson DI, Lowenstein G, Cohen JD. Separate neural systems value immediate and delayed monetary rewards. *Science*. 2004; 306:503-507.
33. Kim-Cohen J, Caspi A, Taylor A, Williams B, Newcombe R, Craig IW, Moffitt TE. MAOA, maltreatment and gene-environment interaction predicting children's mental health: new evidence and meta-analysis. *Molecular Psychiatry.* 2006; 11:903-913.
34. Comings DE, Blum K. Reward deficiency syndrome: genetic aspects of behavioral disorders. *Progr Brain Res*. 2000; 126:325-341.
35. Miles DR, Van den Bree MB, Gupman AE, Newlin DB, Glantz MD, Pickens RW. A twin study on sensation seeking, risk taking behavior and marijuana use. *Drug Alcohol Depend.* 2001; 62:57-68.
36. Fein G, Di Sclafani V. Cerebral reserve capacity: implications for alcohol and drug abuse. *Alcohol*. 2004; 32:63-67.
37. Surti T, Corbera S, Bell MD, Wexler BW. Successful Computer-based Visual Training Specifically Predicts Visual Memory Enhancement over Verbal Memory Improvement in Schizophrenia. *Schizophrenia Research*. 2011; 132: 131-134.
38. Bell, MD, Fiszdon JM, Bryson GJ. Attention training in schizophrenia: differing responses to similar tasks. *Journal of Psychiatric Research*. 2009; 43:490-496.
39. Sheehan D, Janavs J, Baker R, Harnett-Sheehan K, Knapp E, Sheehan M. MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW (M.I.N.I.) Florida: U of Tampa, 2006.
40. Sobell, LC, Sobell, MB. Timeline Follow-Back: A technique for assessing self-reported alcohol consumption. In: Litten RZ, Allan JP. *Measuring Alcohol Consumption: Psychosoical and biological methods*. Totowa, NJ: Humana Press; 1992: 41-72.
41. McLellan AT, Luborsky L, Woody GE, O'Brien CP. An improved diagnostic evaluation instrument for substance abuse patients: the addiction severity index. *Journal of Nervous & Mental Disease.* 1980;168(1):26-33.
42. Flannery, B.A., Volpicelli, J.R. & Pettinati, H.M. Psychometric properties of the Penn Alcohol Craving Scale. *Alcoholism: Clinical and Experimental Research,* 1999; 23(8):1289-1295.
43. Wechsler D. *Wechsler Test of Adult Reading*. San Antonio, TX: Psychological Corporation; 2001.
44. Sandford, J. A., and A. Turner. "Integrated visual and auditory continuous performance test manual." *Richmond, VA: BrainTrain* ; 2002.
45. Reitan RM, Wolfson D. *The Halstead-Reitan Neuropsychological Test Battery: Therapy and clinical interpretation*. Tucson, AZ: Neuropsychological Press; 1985.

46. Wechsler D. *WAIS-III Manual: Wechsler Adult Intelligence Scale-III*. San Antonio, TX: Psychological Corporation; 1997.
47. Wechsler D. *The Wechsler Memory Scale-Revised*. New York, NY: Psychological Corporation; 1987.
48. Brandt J. The Hopkins Verbal Learning Test: Development of a new memory test with six equivalent forms. *Clinical Neuropsychologist.* 2002; 5(2):125-142.
49. Benedict RH. *Brief Visual Spatial Memory Test-Revised*. Lutz, FL: Psychological Assessment Resources, Inc.; 1997.
50. Heaton R. *The Wisconsin Card Sorting Test Manual*. Odessa, FL: Psychological Assessment Resources, Inc.; 1981.
51. Stern RA, Whilte T. *Neuropsychological Assessment Battery: Mazes Test*. Lutz, FL: Psychological Assessment Resources, Inc.; 2005.
52. Patton JM, Stanford MS, and Barratt ES. Factor Structure of the Barratt Impulsiveness Scale. *Journal of Clinical Psychology*. 1995; 51: 768-774.
53. Mercer DE, Woody GE. Individual Drug Counseling. In: *NIDA Therapy Manuals for Drug Addiction Series*. U.S. Department of Health and Human Services / National Institute of Health. Rockville, MD: National Institute on Drug Abuse, Division of Clinical and Services Research. 1999.
54. Siqueland LP, Crits-Christoph JP, Barber et al. The role of therapist characteristics in training effects in cognitive, supportive-expressive, and drug counseling therapies for cocaine dependence. *Journal of Psychotherapy Practice & Research.* 2000; 9(3):123-130.
55. Crits-Christoph PL, Siqueland J, Chittams JP, Barber AT, Beck A, Frank et al. Training in cognitive, supportive-expressive, and drug counseling therapies for cocaine dependence. *Journal of Consulting and Clinical Psychology*. 1998; 66(3): 484-492.
56. Barber JP, Mercer D, Krakauer I, Calvo N. Development of an adherence/competence rating scale for individual drug counseling. *Drug & Alcohol Dependence.* 1996; 43(3):125-132.
57. Alex Pedan, Vasca Inc.,Analysis of Count Data Using the SAS® System, In Statistics, Data Analysis and Data Mining, Paper 247-26,Tewksbury, MA
58. Benjamini Y, Hochberg J. Controlling the false discovery rate: a practical and powerful approach to multiple testing. Journal of the Royal Statistical Society, Series B. 1995; 57 (1): 289-300.
59. Lezak, MD, Neuropsychological Assessment. New York. Oxford University Press. 1983.
60. Yochim, B. P., Baldo, J. V., Kane, K. D., & Delis, D. C. (2009). D-KEFS Tower Test performance in patients with lateral prefrontal cortex lesions: the importance of error monitoring. Journal of clinical and experimental neuropsychology, 31(6), 658-663.
61. Lippa, S. M., & Davis, R. N. (2010). Inhibition/switching is not necessarily harder than inhibition: An analysis of the D-KEFS color-word interference test. Archives of Clinical Neuropsychology, acq001.
62. Beck, Aaron T., Robert A. Steer, and Gregory K. Brown. "Manual for the beck depression inventory-II." *San Antonio, TX: Psychological Corporation* 1; 1996: 82.
63. Beck, Aaron T., and Robert A. Steer. "Manual for the Beck anxiety inventory." *San Antonio, TX: Psychological Corporation*, 1990.
64. Iqbal, Sheikh Usman, et al. "The Veterans RAND 12 Item Health Survey (VR-12): what it is and how it is used." *CHQOERs VA Medical Center. Bedford, MA: CAPP Boston University School of Public Health,* 2007: 1-12.
65. Bell, Morris D. *Bell Object Relations and Reality Testing Inventory: BORRTI*. Western Psychological Services, 2007.
66. Üstün, T. Bedirhan. *Measuring health and disability: Manual for WHO disability assessment schedule WHODAS 2.0*. World Health Organization, 2010.
67. Richardson-Vejlgaard R, Dawes S, Heaton RK, Bell MD. Validity of cognitive complaints in substance abusing patients and non-clinical controls: The Patients Assessment of Own Functioning Inventory (PAOFI). *Psychiatry research*. 2009;169(1):70-74.