D1492-W at RR&D (Palo Alto)
6-1-2014
Cognitive Remediation for Alcohol Use Disorder and Posttraumatic Stress Disorder
NCT02929979

2a. Research Plan

2a.1. Background and Significance

AUD, PTSD and Their Co-occurrence: Relevance to VA and to Treatment

Approximately one third of individuals seeking SUD treatment have PTSD (Ouimette & Brown, 2003) *and compared to civilians, the prevalence of SUD and co-occurring PTSD is elevated among Veterans (Carter et al., 2011; Seal et al., 2011)*. Alcohol is the most common substance of abuse among patients with PTSD, and AUD is the most prevalent and costly SUD among Veterans (CESAR, 2012; SAMSHA, 2012). In fact, as many as 63-76% of OEF/OIF Veterans with an AUD have a co-occurring PTSD diagnosis (Seal et al., 2011). A wealth of research suggests that these disorders are intimately and functionally connected and thus highlights the importance of integrated care (Jacobsen et al., 2001; Schaefer & Najavits, 2007). Unfortunately, despite availability of empirically-supported treatments (EST) for co-occurring SUD and PTSD (Najavits & Hien, 2013), rates of relapse and non-response indicate an urgent need to improve recovery outcomes for this growing and highly vulnerable population.

Compared to individuals experiencing AUD or PTSD in isolation, co-occurrence of the disorders is associated with heightened risk for a host of negative outcomes. Among them include greater PTSD symptom severity, worse occupational, psychosocial and health outcomes, lower reported quality of life, increased interpersonal problems, higher rates of hospitalization and service utilization and increased risk of suicide and mortality (Carter et al., 2011; McCarthy & Petrakis, 2010;Schaefer & Najavits, 2007). In addition, PTSD is a robust predictor of poor SUD treatment response and relapse to drinking (Bradizza et al., 2006; Ouimette & Brown, 2003; Schaefer & Najavits, 2007). Collectively these studies demonstrate that AUD/PTSD patients have poorer clinical and functional outcomes and require more resources to treat than uni-morbid patients (McCarthy & Petrakis, 2010). Accordingly, this population of Veterans represents a critical target for increased attention as they are particularly susceptible to chronic impairment.

In order to advance AUD/PTSD treatment research, it is critical to obtain greater knowledge of the common, trans-disease factors that perpetuate negative recovery outcomes. There is compelling evidence to suggest that neurocognitive dysfunction is one such factor that is amenable to change. Neuroplasticity refers to the natural tendency of the brain architecture to shift and change in response to extrinsic and intrinsic influences (Shaffer, 2012). Remediation of this dysfunction (i.e., harnessing neuroplasticity) may improve recovery outcomes over and above gains associated with current ESTs. Accordingly, in the following sections, we (1) describe overlapping neurocognitive factors known to impede recovery from AUD and PTSD, (2) provide a theoretically-informed conceptual model for how a carefully designed cognitive training program can promote enduring neuroplastic changes in disrupted cognitive processes and reduce chronic impairment, and (3) review evidence for cognitive remediation in psychiatric illness using neuroscience-based cognitive training.

Neurocognitive Dysfunction: An Important Mechanism in AUD and PTSD

Decades of rigorous studies employing mixed and complimentary methodology collectively demonstrate that AUD and PTSD are characterized by similar and overlapping patterns of neurocognitive disruption that engender compulsive and over-trained habitual responding (i.e., alcohol-seeking; escape). These disruptions may predispose individuals to AUD and PTSD as well as perpetuate the disorders (Bomyea et al., 2012b; Gierski et al., 2013). Disruptions will be explained in the context of two systems.

Reward-Seeking System. The etiological underpinnings of AUD and PTSD are rooted in disrupted reward processing (overvaluation of rewarding stimuli) localized in the mesolimbic dopaminergic system (Robinson & Shergill, 2011; Robinson & Berridge, 2000). Over time, with repeated experience, drug and trauma-related stimuli (e.g., alcohol; avoidance-coping) assume disproportionately greater value relative to other rewards (e.g., food, sex) and their "incentive-salience" ultimately functions to diminish capacity for optimal decision-making (e.g., failure to appreciate future consequences despite first-hand experience). As a result of this reward system "hijacking," many addicted and traumatized individuals demonstrate compulsive over-consumption (reward-based habits) and compulsive over-avoidance (threat-based habits). On the surface these habit-based actions may appear irrational and inconsistent with expressed intentions (e.g., abstinence, reduced avoidance; Heatherton & Wagner, 2011; Noel et al., 2010). However, these fast, limbic-driven and impulsive habit-based actions fully align with the neuroplastic changes that have occurred in the brain's reward system. By way of a driving analogy, this system functions as the green-light for reward-driven behavior and signals one to step on the gas, here, in response to alcohol and threat cues.

Prefrontal Impulse Control System. The neuropsychological sequelae of AUD and PTSD include deficits in basic attention, learning and memory and in higher-order cognitive skills known as executive functions (Aupperle et al., 2012; Bates et al., 2013; Polak et al., 2012; Stavro et al., 2013). Executive functions

are involved in the planning, initiation and regulation of goal-directed behavior (Lezak, 1995; Luria, 1966) and they broadly encompass attentional control, inhibition (of automated habit responses), mental flexibility (set-shifting), working memory (mental manipulation of information) and hypothesis generation and problem-solving (Stuss & Benson, 1984). These functions are "seated" in the prefrontal cortex, which is responsible for integrating and interpreting input received from various other cortical and subcortical regions (Miller & Cummings, 2007). Among the many functions carried out by these regions, basic attention, learning and memory are considered most fundamental to optimal executive functioning (Alvarez & Emory, 2006). When compromised (as in AUD/PTSD), individuals are rendered less efficient in executing goal directed behavior because available information is incomplete. To continue with the above analogy, supportive cognitive process (basic attention, memory) help the driver detect cues that signal the need for caution (i.e., yellow light). Executive functions help pump the breaks (i.e., red-light) on impulsive, reward-driven behavior and serve as a steering wheel to change course towards actions with better long-term consequences.

Impulsive and risky behavior, a clinical profile commonly observed in both AUD and PTSD (Brown et al., 2012; Killgore et al., 2008), is considered a manifestation of poor executive control (Bickel et al., 2012). This is because deficits in "supervisory," executive control render it increasingly difficult to combat the automatic habit response unleashed by the reward-seeking system (e.g., by employing positive coping strategies, making a course change; Crews & Boettiger, 2009). Accordingly, in both AUD and PTSD, individuals are more inclined to respond automatically and struggle to redirect attention, problem-solve and consider the long-term consequences of an action (e.g., modify elevated expected reward values that drive habit behavior). For instance, studies of decision-making among individuals with PTSD show that relative to controls, they require more trials to learn an optimal pattern of responding and this is coupled with attenuated activation (reduced expected reward value) in the nucleus accumbens in response to standard (e.g., non-threat related) reward (Iowa Gambling Task; Sailer et al., 2008). AUD is robustly associated with similar patterns of sub-optimal decision-making and impulsive responding (Lejuez et al., 2010) and a general failure to learn from reward prediction errors (Park et al., 2010). Finally, individuals with AUD discount larger future rewards over smaller immediate rewards (i.e., delayed reward discounting) at a higher rate than healthy controls (MacKillop et al., 2011)). Higher delayed reward discounting is also observed in PTSD (Lovallo et al., 2013). To complete the analogy, regular tune-ups to the "braking and gas systems" may help the driver to slow down, evaluate alternative options and select a different route.

Neurocognitive Dysfunction in AUD and PTSD: Relations with Clinical and Functional Outcomes

A wealth of research consistently demonstrates *that compared to healthy control, individuals with AUD and abstinent AUD patients experience greater* deficits in attention, memory and executive functioning (Bates et al., 2013; Moselhy et al., 2001; Scheurich, 2005; Stavro et al., 2013). Indeed, an estimated 50-70% of persons diagnosed with an AUD demonstrate some degree of neurocognitive deficit (Bates et al., 2013). Importantly, among treatment-seeking individuals with AUD, lower executive functioning has been shown to prospectively predict lower treatment compliance and self-efficacy (Bates et al., 2006) and lower overall treatment success (Teichner et al., 2001) as well as post-treatment occupational functioning (Moriyama et al., 2002), relapse status (Noel, 2002), drinking days (Morrison, 2011) and treatment drop out (Teichner et al., 2002). Reviews also demonstrate that deficits in executive functioning among individuals with AUD are associated with higher levels of emotional distress, lower readiness to change and self-efficacy for negotiating high-risk drinking situations, poorer coping skills and greater addiction denial, all of which are critical factors involved in the initiation and maintenance of behavioral change (Bates et al., 2013; Blume & Marlatt, 2009).

Similar to AUD, PTSD is associated with notable deficits in learning and memory and reduced attentional control and executive functioning (Aupperle et al., 2012; Polak et al., 2012). A recent review concluded that deficits are most striking in the domains of attentional control and regulation and response inhibition suggesting that individuals with PTSD experience difficulty disengaging and redirecting their attentional resources (e.g., from threatening stimuli(Aupperle et al., 2012). Indeed, compared to healthy controls and trauma exposed individuals without PTSD, reviews and meta-analyses indicate that those with PTSD tend to demonstrate reduced auditory attention and working memory (i.e., immediate attention, mental manipulation of information), selective and sustained attention (i.e., attending to a long series of presented stimuli), inhibitory functions (i.e., inhibiting an automatic response) and mental flexibility/rapid attention switching (Aupperle et al., 2012; Hayes et al. 2012; McNally, 2006; Polak et al., 2012; Qureshi et al., 2011). Importantly, observed performance deficits are associated with greater PTSD symptom severity (Leskin & White, 2007; Qureshi et al., 2011) and deficits in verbal learning and memory have been shown to predict poor response to PTSD treatment (Wild & Gur, 2008).

In PTSD, the profile of inhibitory dysfunction may specifically relate to re-experiencing and hyperarousal symptoms (e.g., "noisy brain") and contribute to decreased performance on every-day cognitive tasks as well as impaired ability to inhibit emotional memories and physiological arousal (Aupperle et al., 2012; Bomyea et al., 2012a). Observed neurocognitive deficits in PTSD may also foster functional connections with problem alcohol use. Indeed, compromised ability to mentally "switch away" and reorient attention likely increases adoption of avoidant coping mechanisms (i.e., drinking) that mask or "turn down the volume" on what cannot be inhibited. As a result, the inhibitory and attentional networks that require strengthening (as practiced in Cognitive Processing Therapy and Prolonged Exposure), are further neglected (Aupperle et al., 2012).

Cognitive biases are also posited to play a vital role in the development and maintenance of AUD and PTSD (Field & Cox, 2008; Hayes, 2012). Attentional bias refers to the automatic direction of attention towards an external stimulus (e.g., weapons; beer bottle; Field & Cox, 2008). The tendency to automatically gravitate towards and approach a drug cue is termed approach bias (Wiers et al., 2010) and in the case of anxious and fear-related behavioral avoidance, the same principle applies, though in reverse, and is termed avoidance bias (Amir et al., 2012). It is theorized that these cognitive biases subvert and bypass one's explicit desires (e.g., to abstain from alcohol, reduce avoidance) and result in actions that are unaccompanied by conscious reflection (Marteau et al., 2012). More specifically, cognitive biases can function to promote dysphoria and autonomic arousal, increase craving and impulsive urges and ultimately frustrate recovery efforts by weakening cognitive control required for positive coping (Garland, et al., 2011; Hayes, 2012). In fact, cognitive biases are associated with a host of clinically relevant outcomes including alcohol craving, consumption, problem severity and unsuccessful AUD treatment (Field & Cox, 2008; Noel et al., 2010) as well as PTSD symptom severity (Hayes, 2012; Wald et al., 2011). Accordingly, it has been argued that the efficacy of therapeutic interventions employing stand-alone explicit learning strategies (e.g., strategy coaching; reflective processing) are limited to the extent they fail to consider the role of automatic processes that disadvantage individuals in their attempts to achieve behavioral change (Marteau et al., 2012; Vinogradov et al., 2012).

Clinical and Functional Implications of Neurocognitive Dysfunction

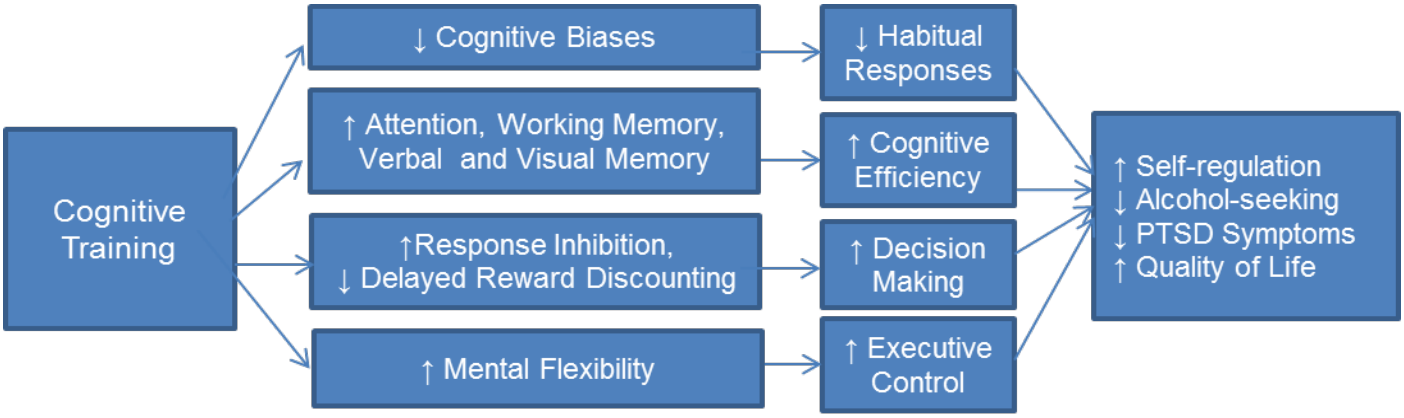
Together, this body of research combines to suggest that individuals with AUD/PTSD experience disruptions in neurocognitive functions (i.e., cognitive bias, attention, learning and memory, inhibition, decision making, mental flexibility) critical for achieving emotional and behavioral control and optimal outcomes. Difficulties with attention, memory and planning, for example, can also represent a major obstacle for patients across many aspects of the recovery process (e.g., navigation of a healthcare system, medication management). Furthermore, clinicians are often poor at identifying cognitive dysfunction among SUD patients (Fals-Stewart, 1997), and ESTs have been slow to recognize and address cognitive dysfunction (Blume & Marlatt, 2009; Carroll et al., 2011). As such, lack of treatment engagement and progress (e.g., failure to do homework; missing appointments; denial and minimization of problem severity) may be inappropriately interpreted as treatment-resistance or lack of motivation. Finally, problematic alcohol use and PTSD are associated with increased risk for cognitive problems later in life (Perreira & Sloan, 2002; Yaffe et al., 2012) and early and targeted cognitive intervention may help protect against these declines. Neuroscience-informed approaches to remediating disrupted cognitive processes may improve clinical and functional outcomes and reduce public health burdens associated with these recalcitrant and highly comorbid conditions.

A Conceptual Model for Cognitive Remediation in AUD/PTSD

As shown in Figure 1, 4 key domains of neurocognitive disruption in AUD/PTSD have been identified for remediation based on the literature reviewed. First, pre-existing cognitive biases to preferentially attend and respond to alcohol-related and threatening stimuli may be lessened with training. This should reduce the strength of triggers and expected rewards and help decrease the likelihood of potent habitual responses (i.e., alcohol-seeking, escape and avoidance behaviors). Second, improvement of attention, working memory and verbal and visual memory is expected to strengthen higher-order cognitive control processes and increase cognitive efficiency. In turn, this will help increase capacity to recognize situations and track cues that signal a potential threat to recovery goals. Third, training of response inhibition and targeting of delayed reward discounting should help to reduce the processes that lead AUD/PTSD individuals to discount future rewards (improved quality of life) in favor of immediate rewards (avoidance, drinking) and result in suboptimal decision making. Remediation of disruptions in this domain will increase the likelihood of temporarily withholding impulsive, stereotypic and overlearned responses and making decisions that factor in long-term consequences. Fourth, increased mental flexibility will equip individuals with enhanced executive control to shift attention away and identify and employ novel, flexible and adaptive strategies. This will help individuals

plan and sequence steps to align behavior more closely with recovery goals. Taken together, we predict that these improvements in cognitive functioning will directly (1) increase patients' ability to self-regulate emotions and behavior, (2) decrease alcohol seeking and use, (3) decrease PTSD symptoms and (4) enhance capacity to effectively implement more adaptive self-management strategies that will ultimately improve quality of life.

Figure 1. Conceptual model for the effects of cognitive training on cognitive functioning and recovery.



Neuroscience-Based Cognitive Training: **Implications for AUD and PTSD**

A number of treatments have been advanced to address neurocognitive dysfunction in SUD populations and include non-computer based cognitive training, physical exercise, transcranial magnetic stimulation and cognitive enhancing medication (Brady et al., 2011; Brown et al., 2009; Herremans & Baeken, 2012; Sofuoglu et al., 2013). Of note, recent technological advances in computerized neuroscience-based cognitive training programs (CNBCTP) have the potential to offer a patient-driven (i.e., performed independently), highly accessible (i.e., web-based), non-medication (i.e., avoidance of side effects and contraindications) treatment alternative to improving cognitive functioning. Further, CNBCTP allow for high levels of individualization to account for each patient's strengths and weaknesses and training exercises can be delivered as state-of-the-art computer "games." These features may render CNBCTP more engaging, appealing and inherently rewarding to participants relative to other cognitive remediation approaches. Indeed, CNBCTP is receiving growing support as an effective means to facilitate recovery from psychiatric illness (Cramer et al., 2011; Macleod, 2012; Vinogradov et al., 2012). Furthermore, such exercises have been shown to ameliorate disrupted cognitive processes in other clinical populations (e.g., schizophrenia, ADHD, aging-adults) that are also observed in AUD and PTSD (Macleod, 2012; Vinogradov et al., 2012). These programs are designed on specific principles of harnessing neuroplastic changes in the distributed neural systems that support cognition and show great potential to optimize recovery outcomes in this highly vulnerable population.

The importance of neurocognitive dysfunction in AUD treatment and the potential for cognitive training has long been highlighted in the alcohol literature and the approach is now considered past the "proof of concept" stage (Bates et al., 2013; Macleod, 2012). In fact, it has even become a research funding priority (NIH, 2010). A burgeoning body of research among non-Veteran SUD populations suggests that cognitive training and cognitive bias modification programs can improve specific functions, that may in turn, enhance clinical and functional outcomes (Bates et al., 2013; Wiers et al., 2013). For instance, Rupp and colleagues (2012) recently reported that cognitive training among an AUD treatment sample was feasible and efficacious in producing improvements in targeted cognitive processes, reducing alcohol craving and improving psychological well-being. Additional studies among heavy drinkers have shown that training to strengthen working memory and response inhibition and weaken automatic action tendencies to approach alcohol are associated with reductions in alcohol consumption (Fadardi & Cox, 2009; Houben et al., 2011a,b; Wiers et al., 2010). A number of other studies support these findings and also suggest that cognitive training in AUD can enhance treatment engagement and commitment and improve long-term recovery outcomes (Eberl et al., 2013; Fals-Stewart & Lam, 2010; Goldstein et al., 2005; Schoenmakers et al., 2010; Wiers et al., 2011).

Cognitive training for PTSD represents a newer area of research and studies are underway to explore its potential in this population (e.g., Seal, 2013, ClinicalTrials.gov). In addition, cognitive bias modification training has been shown effective in reducing anxiety pathology (Hakamata et al., 2010; MacLeod & Mathews, 2012). To date however, no studies have capitalized on available cognitive remediation technologies to comprehensively target patterns of neurocognitive dysfunction that underlie both AUD and PTSD.

Integrative Framework. In this proposal we have outlined evidence to illustrate that improvement in cognitive functioning is a plausible mechanism of change in recovery from AUD/PTSD. This premise is underscored by four key observations: (1) individuals with AUD and PTSD are vulnerable to overlapping neurocognitive disruptions; (2) neurocognitive dysfunction is associated with poor clinical and functional outcomes; (3) recent developments in cognitive training present an exciting opportunity to expand existing technologies to improve cognition functioning and recovery outcomes in this high-risk and vulnerable clinical population; (4) the efficacy of existing empirically supported treatments for AUD/PTSD leaves much room for improvement. The broad objective of the proposed research is to determine whether cognitive training will improve cognitive functioning among cognitively impaired Veterans with AUD and co-occurring PTSD and reduce their alcohol use and PTSD symptoms and enhance quality of life. The proposed research is expected to advance the field by contributing high-quality prospective research on the malleability of neurocognitive dysfunction in AUD and co-occurring PTSD using a neuroscience-based cognitive training program. Given that published studies have already begun to demonstrate that cognitive remediation therapy for AUD and other SUDs is feasible and efficacious, and that there is growing interest in this approach for PTSD, developing a targeted cognitive training approach that is tailored to a co-morbid population is an important and logical next step. Moreover, approaching neurocognitive dysfunction as a trans-disease target for intervention represents an innovative and neurobiologically-informed method for optimizing recovery outcomes. This approach is also consistent with an increasingly prominent model for mental disorders that focuses on common neural systems as opposed to diagnostic categories (NIMH, Research Domain Criteria (RDoC) Project).

Limitations of the current research and how the proposed research aims to fill these gaps. The proposed research plan aims to directly address two notable limitations within the current state of the research. These include (1) limited attention to and identification of common (i.e., "trans-disease") factors that impede recovery from SUD and co-occurring psychopathology, (2) translational and methodological gaps.

(1a) Previous SUD research has suffered from a tendency to ignore the role of co-occurring psychopathology. More recently, scientists and institutions have advocated for research frameworks (e.g., Bickel & Mueller, 2009) and initiatives (NIMH, RDoC Project) to increase recognition and understanding of the common mechanisms and processes that operate across disorders. The goal is to examine the commonalities that transcend any one particular disorder, at multiple levels of analysis, so as to enhance scientific progress among all the disorders in which they operate. Neurocognitive dysfunction has been identified as a trans-disease phenomenon in AUD and PTSD, with potential to be a high-yield target for direct intervention.

(1b) At present there is a surprising dearth of research describing the common cognitive risk-factors that underlie AUD/PTSD or the extent to which they impact clinical and functional outcomes. In the current proposal, we seek to address this gap in the literature by examining relations between cognitive functioning and recovery outcomes in a sample of treatment-seeking Veterans with AUD and PTSD.

(2) The proposed study offers three unique and important translational and methodological contributions:

(2a) Several decades of research have been conducted to pinpoint neurocognitive distortions in the "addicted" and "traumatized" brain. However, few researchers have capitalized on this knowledge-base for clinical translational purposes to develop novel treatments to improve cognition. The proposed study is the first to offer a neuroscience based translational framework to remediate neurocognitive disruptions identified in the literature. Furthermore, although neurocognitive dysfunction is well-documented in PTSD, remediation of these affected processes represents a newer area of inquiry in this population. The proposed study will employ a cognitive training approach, shown to be effective in improving cognitive functioning in other clinical populations (e.g. schizophrenia), which also encompasses training modules that directly target neural processes and functions disrupted in both AUD and PTSD. These scientifically-informed modules have been iteratively developed by an experienced multidisciplinary research team.

(2b) Studies with AUD populations have tended to target either cognitive biases or executive cognitive functions (e.g., working memory) but not both (as is proposed). Given the complicated nature of these conditions, simultaneous targeting of these core neurocognitive processes is important as they do not appear in isolation among affected individuals. The proposed research therefore represents a novel and important first step in translating basic laboratory research into intervention as no previous study has simultaneously and comprehensively targeted PTSD and AUD pathology with neuroscience-based cognitive training.

(2c) The proposed study will address a tendency in the literature to create functional boundaries between different SUD research methods, by employing a multi-modal assessment of primary outcomes. Four levels of measurement will be incorporated: structured interviews, self-report measures, standardized

neuropsychological test batteries, and computerized behavioral tasks. This multi-modal assessment will function as a translational, integrated framework to demonstrate how measures of cognitive functioning, spanning from the neurocognitive to the self-report level, correspond in this population.

Significance and relevance to VA patient care mission and advancement of clinical practice. The proposed work is well aligned with the VA's evidence-based paradigm-shift to integrate substance abuse treatment into mental heath services and is directly relevant to Veterans' health in 4 key ways. First, there is limited research on how cognitive dysfunction impacts recovery outcomes among Veterans with AUD and PTSD and this is problematic given the high rate of comorbidity. Findings from the proposed study will help direct VA resources to improve mental health treatment by providing rich and multi-modal recovery outcome data for this population. For instance, I will use the proposed research to help provide a framework for the development of cognitive screenings and interventions for Veterans with SUD and complex comorbidities. Identification of cognitive dysfunction could afford VA clinicians the opportunity to modify intervention delivery and preemptively recruit organizational and community resources. In addition, I will use these results to inform initiatives to tailor substance abuse treatment programs to better address impediments posed by cognitive impairment (e.g., external memory cueing systems; visual, computer-assisted presentation of clinical materials). Second, findings from the proposed study will determine the malleability of mechanisms that can be targeted to potentially improve recovery outcomes among this vulnerable, highly relapse prone, comorbid population. In turn, improved recovery outcomes would reduce risk of chronic impairment and potentially free up resources to treat new incidences of SUD and PTSD with a reduced treatment entry delay. Third, there are important trans-diagnostic implications related to the proposed research including shared cognitive risk-factors that underlie the comorbidity between PTSD and problematic alcohol use, specifically, and anxiety-substance comorbidity more broadly. Gaining a better understanding of the common processes and mechanisms that operate in these disorders will provide clinicians a richer conceptualization of the development, maintenance and treatment of this comorbidity in VA. Fourth, the use of a home-based, patient-driven recovery tool is consistent with the VA's recovery model, which focuses on a gradual reduction in reliance on daily activities in treatment settings. Adjunctive web-based rehabilitation technologies may also help foster patient recovery in cases where staffing, space, acceptability of counseling, and transportation are barriers.

2a.2. Preliminary Studies

My program of research leading up to this application has focused on the relationships between substance use, cognition and emotion, particularly in the context of co-occurring psychopathology. Below is an overview of representative research projects which have culminated in the proposed study. Additionally, *two* studies are reviewed which provide pilot data for the current proposal.

Cognitive and neurobiological mechanisms of alcohol-related aggression. (Heinz et al., 2011; *Nature Reviews Neuroscience.* See Appendix). This multidisciplinary review provided several layers of cognitive and neurobiological evidence to help explicate the pathways by which individuals with AUD are at increased risk for impulsive and aggressive behavior. It also highlighted the mediating role of individual differences in executive functioning that may account for why some individuals become aggressive and violent under the influence of alcohol whereas others do not.

Quantifying demand and reinforcement for psychoactive substances in humans*, (*Heinz et al., 2012; *Current Drug Abuse Reviews,* PMID 23062106, NIH Open Access)**.** This comprehensive review detailed how behavioral economic theoretical frameworks and measurement tools can help explicate complex addictive processes (e.g., irrational decision-making; devaluation of future rewards) that frustrate recovery. In addition, the review provided a translational platform for development of clinical interventions that target sub-optimal decision making, a facet of cognitive dysfunction, in substance use disorders.

Problem alcohol use among individuals with HIV: Relations with everyday memory functioning and HIV symptom severity (Heinz et al., 2013, *AIDS & Behavior,* PMID 23979498)**.** This study examined the impact of problematic alcohol use (PAU) on different aspects of everyday memory functioning (EMF) among a sample of HIV-infected individuals. Results indicated that even after controlling for HIV symptom severity, PAU explained significant variance in self-reported difficulties in memory functioning, retrieval (e.g., forgetting events, prospective memory), conversational monitoring (e.g., repeating oneself) and memory for activities (e.g., what you did yesterday); further, EMF mediated the relation between PAU and HIV symptom severity.

Pilot #1: Enhancing Cognitive Function in OEF/OIF Veterans with PTSD Using Computer-Based Cognitive Training. Data were collected on 5 Veterans who were randomly assigned to receive 40 hours of home-based cognitive training (n=2; *Posit Science*) or a computer-game control (n=3; *Sporcle.com*) over 8 weeks. Findings indicated that participants in the cognitive training group appeared to demonstrate increases in working memory (1, 2), verbal learning and memory (3) and response inhibition (4) pre to post-training (3-month follow-up), *whereas no changes were observed for the control group. Participants also completed self-report questionnaires about the extent to which they found the computer games engaging, enjoyable and challenging. Responses appeared similar across the training and control conditions. In addition to observed changes in cognitive outcomes, this project has allowed us to identify logistical obstacles that may occur in the proposed CDA-2. For example, participants reported that they did not like having to sit in front of a desktop computer for an hour and wanted training to be more portable. Participants also reported that 40 hours was somewhat burdensome. Accordingly, experience from this project has guided our decision to include 30 hours of training over 6 weeks delivered via a mobile computing device so as to reduce participant burden and increase accessibility and portability of training. Overall, this pilot study demonstrates that a similar target population of Veterans can be recruited into a cognitive training protocol and can successfully adhere to and complete both arms of the study and attend follow-up sessions.*

M(SD)	**Pre Training**	**Post Training**	***Pre Control***	***Post Control***
1) Auditory Consonant Trigrams	25.5 (14.85)	40.5 (6.36)	*29 (7.55)*	*30(12)*
2) Wechsler Adult Intelligence Scale-IV Digit Span	9 (1.4)	12 (2.8)	*7(2)*	*7.6(.58)*
3) Wechsler Memory Scale-IV Verbal Paired Associates	9 (2.83)	11.5 (2.12)	*9.67(2.08)*	*10.67(2.08)*
4) Delis-Kaplan Executive Function System Stroop Test	6.5 (7.78)	12 (2.83)	*9.67(.58)*	*9.67(2.08)*
5) Engaging and Enjoyable (1 = not at all – 10 = extremely)	-	*8 (0)*	-	*7 (2.65)*
6) Challenging (1 = too easy – 10 = too challenging)	-	*6.5 (.71)*	-	*7.67(2.08)*
7) Hours completed	*32.79 (5.98)*		*31.38 (7.54)*	

Pilot #2: Protocol Acceptability and Feasibility and Cognitive Training Usability Testing Among Veterans with AUD and PTSD. *Five male Veterans (Mage = 39, SD = 8.9; 3 Caucasian, 1 African American, 1 Asian) with AUD and PTSD were recruited from SUD and PTSD treatment programs, in a one month period, to complete a comprehensive neuropsychological and psychiatric baseline assessment, 8 individual cognitive training usability testing sessions and an immediate follow-up assessment. The objectives were to (1) assess acceptability and feasibility of the study protocol (including recruitment) and (2) determine initial impressions of the BrainHQ study site tailored for treatment-seeking Veterans with AUD and PTSD and to isolate potential problematic areas in the software. At protocol completion (n = 3 to date), user responses on a Likert-type scale (0 = not at all; 10 = extremely) indicated that the trainings were enjoyable (M = 6.7, SD = 0.58), challenging (M = 6.3, SD = 1.5) and engaging (M = 7.0, SD = 1.0). Using an agreement scale (1 = strongly disagree, 7 = strongly agree), users tended to indicate that they (1) believed the trainings to be helpful to their health (M = 5.0, SD = 1.0), (2) would recommend the trainings to a friend (M = 5.3, SD = 0.58), (3) would spend 1 hour a day completing the trainings (M = 5.0, SD = 1.0), (4) would be willing to complete 30 hours of training over 6 weeks (M = 5.3, SD = 1.2), (4) would prefer to complete the trainings on a portable computing device (M = 5.0, SD = 1.7), (5) would prefer to complete the trainings at home (M = 4.7, SD = 1.5) and (6) could safely return a loaned portable computing device (M = 6.7, SD = 0.58). In terms of the training website, participants used the same agreement response scale, and again tended to indicate that the training website was well-organized (M = 5.0, SD = 0) and easy to use (M = 5.0, SD = 1.0) and they felt comfortable using it (M = 5.7, SD = 0.58). Participants also generally indicated that the training exercise instructions were clear and easy to understand (M = 4.7, SD = 1.2) and that they were satisfied with the web-site interface (M = 5.0, SD =1.0).*

Testing session observations and participant feedback suggest that provision of instructions in both written and oral format may be beneficial in this population and that individual exercises should be delivered in greater variety and in shorter time segments to enhance participant engagement. In addition, pacing of certain exercises (e.g., inter-trial intervals) could be modified to reduce the potential for fatigue. Finally, navigation of the training portal was found to be enhanced by features that allowed for completed exercises from previous training sessions to be grayed out/frozen These sessions have also allowed us to determine potential

variability in amount of time required to complete exercises within each training day. This pilot work demonstrates that several aspects of the cognitive training intervention can be optimized for an AUD-PTSD population. Moreover, our recruitment rate (i.e., 5 participants in one month) and retention success provides additional evidence for the overall feasibility of the proposed research.

2a.3. Research Design and Methods

Design Framework.

The proposed research is a 2-stage prospective longitudinal investigation. It will investigate the impact of a tailored neuroscience-based cognitive training program (BrainHQ) on cognitive functioning and clinical and functional outcomes among Veterans with AUD and co-occurring PTSD, recruited from an outpatient SUD treatment program. The iterative design is based on guidelines put forth by the Stage Model of Behavioral Therapies per the National Institute on Drug Abuse (Carroll & Onken, 2005; Rounsaville et al., 2001). In both stages, Veterans will be randomized to receive either a computerized cognitive training or a computer-game control. Stage 1 ("Stage1a feasibility") will recruit 20 Veterans to examine and improve acceptability of both conditions and test and improve the usability of the computerized cognitive training program. The aim of Stage 1 is to inform efforts to maximize feasibility for Stage 2. In Stage 2 ("Stage 1b efficacy"), *128* Veterans will be recruited (Stage 1+2 recruitment = *148*). The aim of Stage 2 is to examine the efficacy of cognitive training, as compared to a control condition, for improving cognitive functioning as well as alcohol, PTSD, and quality of life outcomes. Participants will complete 30 hours of web-based computerized cognitive training or computer games over 6 weeks, at a rate of 5 hours per week. In both stages, participants will complete a clinical and neuropsychological assessment battery at intake (baseline assessment), immediately following six weeks of training (post-training assessment), and *6-months post-training (follow-up; Stage 1 follow up is 3 months)*. In addition, in each week of the training period, participants will complete assessments (e.g., alcohol and substance use, mood) and check-in with research staff on their engagement in the training.

2a.3.a. Limitations to the proposed procedures and alternative approaches to achieve the specific aims. The first design consideration involved the selection of the outpatient SUD program for participant recruitment, as opposed to inpatient SUD treatment or PTSD treatment or non-treatment seekers. Recruitment from this treatment context is expected to improve the generalizability of our findings and allow for early coordinated intervention. Indeed, 89% of treatment-seeking SUD patients receive outpatient care (Office of Applied Studies, SAMHSA, 2006) and Veterans with co-occurring SUD and PTSD are typically seen for SUD treatment prior to enrollment in PTSD treatment. Inclusion of outpatients (as opposed to inpatient) will also increase sample variability in terms of AUD and PTSD severity. Finally, outpatient SUD treatment programs are not only more prevalent within VA, but are more cost-effective, thus providing an 'ideal' framework for the future implementation of adjunctive cognitive remediation programs based on findings from the proposed study. In addition, given the early stage of research development, and the potential impact of daily heavy drinking on training engagement, it was important to optimize study feasibility by targeting treatment-seeking individuals in early recovery as opposed to non-treatment seekers.

The second design consideration focused on the SUD sub-population of individuals with AUD. We chose to focus the study on individuals with a primary diagnosis of AUD, as opposed to other SUDs, for three reasons. (1) AUD represents the most common SUD within VA (CESAR, 2012; SAMSHA, 2012); (2) The preponderance of extant research on cognitive training in SUD has been conducted among AUD populations (Bates et al., 2013), thus providing a basis for a clear extension to AUD populations with PTSD; (3) Deficits in specific cognitive functions have been shown to differ as a function of SUD type (Van der Plas et al., 2009), making comparison across different primary SUDs potentially difficult. Therefore, it was important to limit sampling to individuals with a primary diagnosis of AUD so as to avoid type II errors due to limited power to detect differences between AUD and other SUD groups in terms of the hypothesized aims. If successful, future work will extend the present findings to other SUD populations.

The third design consideration involved the decision to target multiple cognitive domains as opposed to a single domain. This will preclude ability to discern how individual training modules differentially contribute to proposed outcomes. However, future studies can assess this question by dismantling the training protocol to determine which components may be more effective in improving cognitive function.

The fourth design consideration involved the decision to deliver a mobile, home-based intervention as opposed to clinic-based. This decision was grounded on formally documented preferences of participants in seminal studies by secondary mentor, Dr. Vinogradov's (e.g., 79 out of 80 participants elected to train at home via laptop over training in the clinic),procedures currently employed in Dr. Seal's (consultant) home-based

cognitive training intervention among Veterans with PTSD *and results from our pilot work*. Although there is potential for theft or loss of mobile computing devices, Dr. Vinogradov's devices have been consistently returned. Thus, based on Dr. Vinogradov's experience, it has been feasible to loan devices to clinical populations. See human subjects for comprehensive description of data and device security precautions. Furthermore, completion of training at home rather is consistent with a recovery model and may also be less stigmatizing. Finally, mobile health technology options may be more appealing to patients with multiple competing priorities and geographical and transportation barriers.

The fifth design consideration involved the "dose" of cognitive training to be administered. Previous research in schizophrenia populations has demonstrated that a signal may be detected at 20 hours (Keefe et al., 2011) though prolonged benefits (i.e., enduring cortical changes) require longer training periods (e.g., 50-80 hours; Vinogradov et al., 2012). Cognitive training studies among AUD populations have employed highly variable training durations (2-20 hours) and schedules (4 to 25 sessions) and this variability appears to be driven by the nature of the exercises and the number of cognitive processes targeted (Fals-Stewart & Lam, 2010; Goldstein et al., 2005; Houben et al., 2011a; Rupp et al., 2012; Schoenmakers et al., 2010). Based on the training durations and associated gains previously observed in AUD populations (e.g., Bates et al., 2013), as well as the number of domains to be targeted and the associated exercises we will employ, we chose 30 hours as an optimal dose of training in the current study. Thirty hours will permit us to deliver approximately 7.5 hours of training targeting each of the 4 general cognitive domains illustrated in Figure 1 above.

The sixth design consideration was not to power the Stage 2 sample size to test whether change in cognitive outcomes mediates the relation between cognitive training (vs. computer game control) and recovery outcomes. Based on the early stage of research development ("Stage 1b efficacy"), we decided that powering the sample size for tests of mediation is not feasible or within the scope of the proposed research.

The seventh and final design consideration involved the decision to include individuals with comorbid Axis-I disorders (except Psychotic Disorders and Schizophrenia). Importantly, because AUD and PTSD are highly comorbid disorders, findings from the proposed study would dramatically suffer from limited generalizability should individuals with comorbidities be excluded from participation. Instead, Axis-I disorders and non-alcohol SUD will be comprehensively assessed and if necessary, controlled for if randomization procedures do not evenly disperse participants with comorbidities across conditions.

2a.3.b. Study Settings

The proposed study will recruit participants from the outpatient SUD treatment program at the Menlo Park Division of the VAPAHCS. In FY12, 94% of patients at the clinic were male and 18% were OEF/OIF Veterans (VA PERC, Personal Communications). The outpatient SUD program is staffed with medical providers (e.g., psychiatrists, nurses) and a psychological support team (e.g., addiction therapists, psychologists) and uses a treatment model that includes both individual and group therapy. Although time to discharge varies in outpatient treatment, 3 months is the minimal intended dose of SUD treatment based on VA/DoD clinical guidelines. As observed in past VA-funded projects of the mentors of this proposal, the close proximity between study personnel and the treatment program (located on the grounds of the Menlo Park VA) facilitates communication and adherence to project procedures and thus, increases the overall feasibility of the proposed work (see also letter of support from program director Dr. Potoczniak). Participants will complete the training portion of the study off-campus, in the privacy of their homes or in another location of their choosing.

Treatments Administered: The outpatient SUD treatment program within VAPAHCS is consistent with outpatient SUD programs throughout VA. This program provides SUD care within a multidisciplinary and integrated treatment program. The therapeutic modality of most VA SUD outpatient programs, including the program at the Menlo Park VA, is predominantly group-based (VA PERC, Personal Communications). Patients do not need to detoxify prior to treatment entry and the program provides a typical patient with approximately 4 days of weekly treatment (approximately 4 hours per day). All patients receive approximately 10 hours of group therapy per week in addition to individual psychotherapy. All patients are screened for PTSD upon admission. Broad treatment of all substance dependence, including alcohol, is the primary aim of the program with major treatment components including: didactic education, motivational enhancement, cognitive-behavioral therapy for relapse prevention, and integrated therapy for SUD and PTSD (e.g., Seeking Safety); approximately 90% of the patient population engages in mutual self-help groups (e.g., 12-step).

2a.3.c. Recruitment Procedures.

Clinicians will provide a descriptive study flyer to patients newly accepted and enrolled into the outpatient SUD Program, with a diagnosis of AUD and PTSD (based on information collected through intake

assessment procedures). Individuals reporting interest in the study will be asked for verbal consent to be contacted by a research assistant (RA). In addition, informational flyers will be posted throughout the clinic with a toll-free study phone number listed for interested participants to call. A member of the research team will contact prospective participants to provide an explanation of study procedures and to complete a phone-based screening. The RA will schedule a lab-based screening visit should the individual meet basic eligibility requirements. Drs. Trafton and Bonn-Miller (mentors) have long-standing relationships with administrators and clinicians in the outpatient SUD program and have worked closely with them to successfully collect program evaluation data and recruit patients to participate in research.

Size of the proposed recruitment sample was estimated based on: (1) mentor experiences conducting research with similar screening procedures, designs and populations and in similar treatment settings; (2) attrition rates reported in the literature in cognitive training protocols with alcohol populations. For example, Dr. Bonn-Miller (secondary mentor) has conducted an intensive longitudinal study with Veterans from the VAPAHCS outpatient SUD treatment program with Cannabis Dependence and PTSD. He achieved an 85% participation rate (104 acceptances, 19 refusals) and demonstrated, among 104 eligible cannabis dependent participants (41 with co-occurring PTSD), 66% retention at 6-month follow up. In terms of lab-based screening, based on mentors' experiences and estimates in the literature (e.g., Bates et al., 2013), we expect to screen approximately *222* individuals in order to obtain *148* eligible participants. In terms of attrition, previous cognitive training studies in alcohol populations have had dropout rates anywhere from 0% to 45.7% (e.g., Fadardi & Cox, 2009; Goldstein et al., 2005; Houben, et al., 2011a; Rupp et al., 2012; Schoenmakers et al., 2010). Accordingly, a conservatively estimated total recruitment sample of *148* will allow for up to 30% attrition in each stage, resulting in a final sample size of approximately *110* Veterans.

2a.3.d. Participants. A total sample of *148* male and female (10% female; n = 20 Stage 1, n = *128* Stage 2) Veterans with a diagnosis of AUD and PTSD will be recruited from the outpatient SUD treatment program at VAPAHCS. In FY2012, 4,270 unique patients were treated in this program and 700 met criteria for AUD and co-occurring PTSD (PERC, Personal Communications). Based on these data, the sample will be feasible to recruit by the *middle of year 5* (see section 2a.3.k. "Timeline for Primary and Secondary Research Activities").

2a.3.e. Inclusionary and Exclusionary Criteria. For inclusion in the study, participants must: (1) be a Veteran 18-65 years of age and enrolled in outpatient SUD treatment within VAPAHCS; (2) meet DSM-*5* diagnostic criteria for current AUD and seeking treatment for AUD; (3) meet DSM-*5* criteria for current PTSD; (4) be willing to perform daily home-based computer exercises for 6 weeks; (6) demonstrate at least a mild "cognitive deficit" (i.e., at least 1 SD below the mean) in at least one cognitive domain of the neuropsychological test battery administered during the screening visit (see Table 1). Individuals will be excluded based on evidence of the following: (1) history of, or current, psychotic disorder or Schizophrenia; (2) current scheduled (i.e., daily) prescribed use of cognitive enhancers (e.g., Memantine) or stimulants (e.g., Methylphenidate) that may enhance cognitive performance; (3) current severe traumatic brain injury (DoD TBI Screen ≥ 2); (4) any type of dementia (Mini Mental Status Exam (MMSE) < 24), delirium or medical illnesses associated with potential cognitive issues (HIV, Hypothyroidism, B-12 deficiency); (5) any level of mental retardation (Wechsler Test of Adult Reading WTAR); (6) Limited ability to speak/read/write/understand English (WTAR); (7) Inadequate vision or hearing; (8) Active suicidal/homicidal intent. Self-report and collateral history from medical record/primary care physician/outpatient addiction treatment team will be used as necessary to determine inclusion and exclusion. Suicidal and homicidal intent will be assessed in the context of a structured clinical interview (see section 2a.3.i for details). In the unlikely event that respondents endorse active intent they will be referred immediately for treatment and will be excluded from the current study (See "Human Subjects" for specific details on safety protocol).

2a.3.f. Participant Retention. The retention component of the study is informed by recommended strategies in the literature (Scott, 2004) and the training team's wealth of experience running similar studies.

Financial Incentives. Please see Figure 2 for the compensation schedule. Participants will be compensated in gift cards for their time after each completed visit. In addition to payment for study participation, *participants will receive $5 for every completed training session (up to $25 a week; $150 total) to further optimize engagement in the protocol*. Participants can therefore earn up to a total of $*350* for full study participation. These payments are not contingent upon alcohol use status and this will be carefully explained to participants to avoid potential response biases. Participants who complete training will also be presented with a personalized certificate of completion.

Tracking, General Contact, Check-ins. Throughout the course of the study simultaneous strategies will be employed at the management, staff and participant levels to maintain participant contact and to maximize fidelity to the training protocol. First, during the initial screening assessment a Locator Form (Hall et al., 2003) will be completed for each participant that includes: (1) home address, (2) email address, (3) home/work /cell phone numbers, (4) employment or school information, and (5) contact information for two additional individuals to be used if contact with the participant is lost. Tracking information will also be collected at all follow-up interview points. Second, based on strategies successfully employed by Dr. Seal's (consultant) research team at SFVA conducting a cognitive training study among Veterans with PTSD, an RA will meet with participants each week (directly following their laboratory assessments) to check in and review level of training engagement (telephone contact will be arranged otherwise). If necessary, the RA will help participants problem-solve around barriers to completing trainings. Check-ins are intended to facilitate adherence to the training protocol so that participants may derive maximal benefit. Additional methods to help reduce attrition will include specialized cards (e.g. birthday cards) which will includes a change of contact information form and a toll free number of the study center for subject-initiated contact (Leonard et al., 2003).

Reminders: A reminder call will be placed the day prior to participants' scheduled in-lab assessment. Research staff will mail a reminder to participants one week prior to their follow-up appointment.

2a.3.g. Data Collection Procedures. Recruitment will target Veterans with AUD and co-occurring PTSD in the outpatient SUD treatment at PAVAHCS (see section **2a.3.c.)**. To insure against acute alcohol intoxication, participants will be required to provide a Breath Alcohol Concentration (BrAC) of .00 prior to the beginning of each study visit. Should participants exceed this cut-off, they will be rescheduled for the following business day. Research staff will be trained on manualized assessment procedures and regularly observed by Dr. Heinz (supervised by Drs. Sullivan and Bonn-Miller) and regular meetings will be held to discuss testing and scoring questions. Inter-rater reliability will be determined with regularity throughout data collection. Staff administering the neuropsychological batteries will be blinded to participant condition.

During the screening assessment, participants will provide written informed consent. Next, a more detailed assessment of inclusionary/exclusionary criteria will be conducted (see section 2a.3e. Measures) and participants will be compensated $30 for completion of this screening assessment. Individuals not meeting inclusionary criteria will be excluded from the remainder of the study. Individuals meeting all criteria will be scheduled to return for a baseline assessment. More specifically, participants will be administered structured clinical interviews, self-report questionnaires and remaining neuropsychological assessments, to collect baseline levels of responding. Participants completing the baseline assessment will be compensated $50. Participants will be randomized in a 1:1 ratio to condition (training or control) and a checklist will be used to ensure that all study criteria are met before randomizing a participant. Participants will return to the lab the next business day for orientation to cognitive training (or computer game control) procedures and will be issued a loaned computing device (for descriptions of training schedule and platform delivery see section 2a.3.h. Method Overview). Participants will be compensated 10$ for completion of the orientation session. Over the course of 6-weeks, participants will complete 30 hours of home-based cognitive training or computer games at the rate of 5 hours a week. *Participants will earn $5 for each completed training session (up to $25 a week; $150 total).* Participants will be asked to refrain from alcohol or other substance use at least 4 hours prior to and during completion of training exercises. They will be advised that it is best to work on the programs in a quiet, preferably private location. Participants will log-in to a web-based cognitive training program or gaming site using a number assigned to their loaned wireless equipped computing device. Participant's engagement (i.e., adherence) and performance data will be sent to a secure server (i.e., no participant identifiers or personal health information); the data uploaded on the server will be identified only by the participant's assigned device number. A de-identifier sheet linking the device number to participant will be locked in the lab with access limited to study staff (See "Human Subjects" for specific details regarding the data security protocol). Participants will return to the lab at the end of each training week (i.e., 5 visits) to complete self-report measures and participate in check-ins with the study coordinator regarding their level of engagement in the protocol. Participants will be compensated $10 each study week they complete their lab-based session.

A post-training assessment will be conducted directly following completion of the 30-hour cognitive training or computer game control schedule at week 6. Post-training assessments will include interviews, self-report questionnaires, and an abbreviated neuropsychological test battery. Upon completion of the post-training assessment, participants will be compensated $30 and contact information will be collected for use in scheduling the post-training follow-up. Finally, participants will complete the post-training follow-up assessment *(3 months Stage 1; 6 months Stage 2)*, which will be comprised of the same measures administered in the

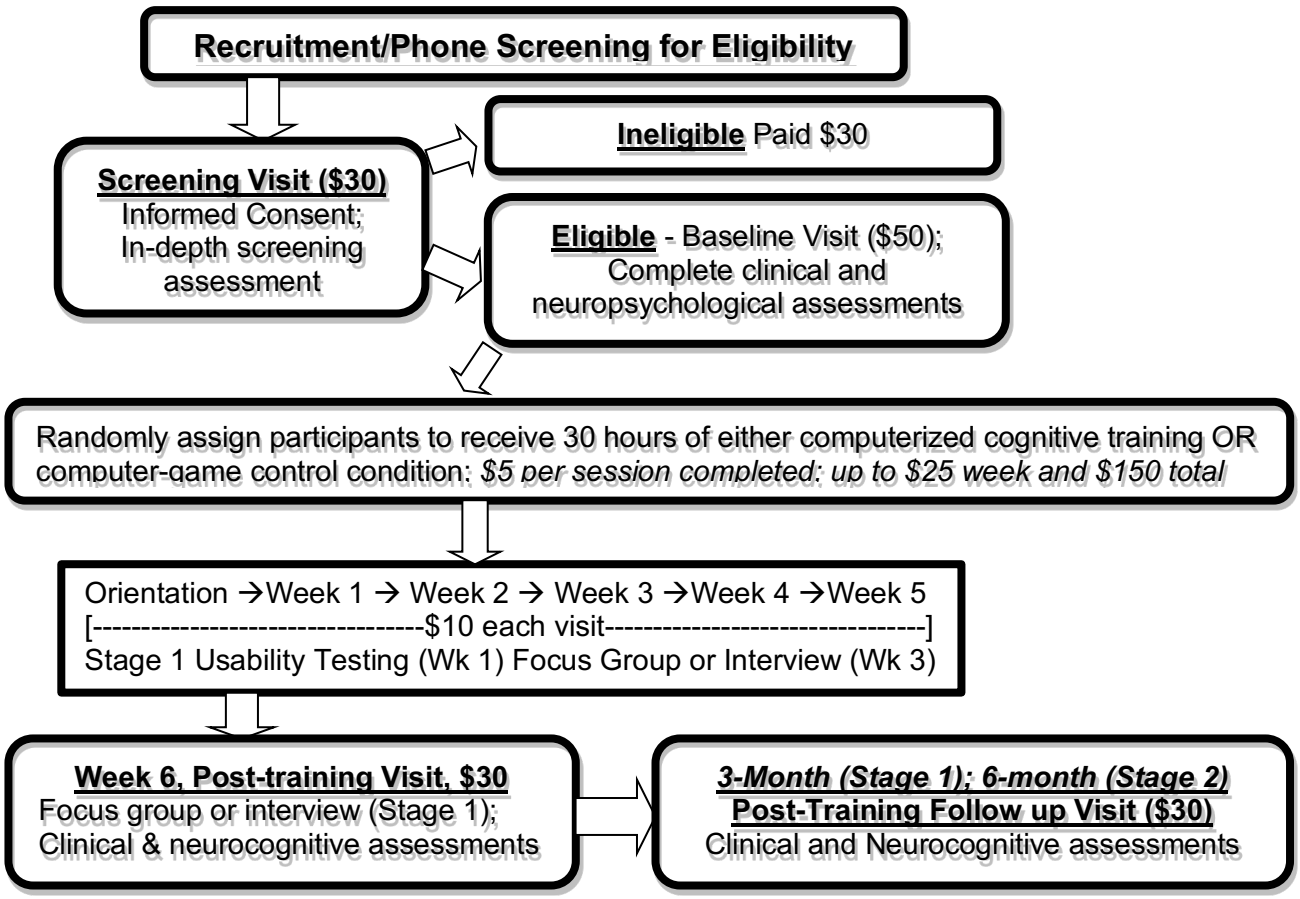
post-training assessment. For individuals within the greater Bay Area, follow-up assessments will be conducted in-person. For those unable to return to VA-MPD, portions of the follow-up assessment will be conducted via phone and mail. All assessments will be conducted by trained RAs and supervised by the PI and training team. Participants will be compensated $30 for this follow-up session.

2a.3.h. Data Collection Procedures Overview.

Method: *Overview; Training and Control Content and Procedures.*

A multi-modal method of assessment will be utilized to measure all variables in the current study. This will include the use of self-report questionnaires, clinical interviews, neuropsychological testing and behavioral tasks. The measures to be employed are outlined below in relation to the construct being assessed. Participants in Stage 1 will complete the same battery and schedule of measures, and receive the same schedule of compensation as participants in Stage 2. Stage 1 specific procedures are outlined below.

Figure 2. Overview of Procedures.



Stage 1 will include collection of qualitative and quantitative data that will be used to (1) assess and improve acceptability (e.g., satisfaction; protocol adherence) of cognitive training and computer game control conditions and, (2) test and improve usability of the cognitive training program. The goal of Stage 1 is to identify potential barriers and ensure that participants can carry out the intended tasks effectively, efficiently, and satisfactorily so as to maximize feasibility for Stage 2. Initial usability testing will be conducted to expose any difficulties participants may have navigating the cognitive training exercises via computer. Participants randomized to receive cognitive training will be introduced to exercises in the Human Computer Interaction Laboratory located in the CHCE (see letter from Dr. Trafton). User interaction with the cognitive training exercises will be taped using instrumented software (i.e., Morae, Techsmith®) to record user navigation of the program. Dr. Heinz and a research assistant will monitor user interaction with the web-site, carefully documenting any navigational or instruction comprehension challenges. A brief semi-structured interview will then be conducted to probe users about their satisfaction with the cognitive training exercises and to elicit feedback about features that could be addressed through modifications to the system. Midway through training (week 3) and post-training (week 6), we will administer usability and acceptability questionnaires and conduct semi-structured interviews or moderated focus-groups, should condition enrollment size permit, to ask about user experience and elicit

feedback for further refining usability of the cognitive training and improving adherence to and satisfaction with both study conditions. Specifically, participants will be asked questions about how easy the system is to use, how the system fits into other clinical care, how they felt about the training schedule and mode of delivery, how they interact with the system, and whether they are satisfied with the system or if they perceive benefits. *Please see Appendix for examples of these measures.* In addition, we will use protocol adherence data (i.e., trainings completed) to further inform our efforts to increase acceptability. Data collected in Stage 1 will be used to optimize protocol feasibility prior to beginning Stage 2.

Training Schedule and Delivery. Participants will be randomized to receive either 30 hours of a computer game control condition or a computerized cognitive training, over 6 weeks, at a rate of approximately 5 hours per week. The cognitive training and computer game-control conditions will be delivered on a loaned, wireless-enabled computing device, the Apple iPad 2. This device will come equipped with 3G radios/wireless hotspots to make use of cellular data networks in order to ensure broad accessibility to both web-based programs.

Computerized Cognitive Training: Participants will complete 30 hours of cognitive training exercises using a web-based program, BrainHQ (BPI/Posit Science, San Francisco; see letter of support from BPI/Posit Science). BrainHQ (https://brainhq.positscience.com see Appendix) is based on a previous neuroscience-based cognitive training program shown to improve cognition and self-rated health in two large randomized controlled trials with community-dwelling older adults (Smith et al., 2009; Wolinsky et al., 2010). In addition, a randomized controlled trial by Vinogradov and colleagues demonstrated that schizophrenia patients made significant gains in general cognition and verbal learning and memory as a result of training, and improved cognition was associated with improved quality of life (Fisher et al., 2009; Fisher et al., 2010). Moreover, fMRI studies by Vinogradov and colleagues with schizophrenia patients indicate that cognitive improvements in response to an extended version of this program are associated with "normalization" of brain activation patterns in prefrontal cortical regions during reality monitoring and verbal memory tasks, further supporting the notion that cognitive training generates positive plastic brain changes (Subramaniam et al., 2012). At present, a version of the BrainHQ program is being employed in Dr. Seal's (consultant) cognitive training clinical trial of Veterans with PTSD. Given that AUD and PTSD, like schizophrenia, are associated with deficits in attention, memory and cognitive control, we posit that intensive neuroplasticity-based cognitive remediation training using the BrainHQ program has strong potential to improve cognition in this population.

We will use a suite of BrainHQ exercises specifically designed to target and ameliorate disruptions in the 4 general domains described in Figure 1. We will employ basic exercises that focus on increasing processing efficiency in the auditory and visual perceptual and working memory domains, as well as exercises that target impulsivity and cognitive biases. Exercises will be packaged into 4 modules (attention skills, memory skills, executive functioning skills, cognitive control skills) comprised of 4 exercises each. All participants will progress through the same fixed schedule of modules. In each module of training, participants must improve the speed and accuracy of their responses in the targeted cognitive domain of interest. Participants are rewarded on correct trials with points and animations for their performance. Exercises continuously adjust difficulty level to user performance to maintain an approximately 80% correct performance rate. This "Bayesian adaptive" approach, in which the stimulus level at each trial is determined by the participant's responses from all previous trials, determines the level of maximum training efficacy. Compliance and performance will be monitored by data upload following each training session.

Computer Games Control Condition: Participants will play a rotating set of commercial computer games *(see Appendix)* at the same dose and frequency as the cognitive training. We selected this control activity because it mirrors the game-like properties of the cognitive training and it will be used to control for contact with research personnel and for the non-specific effects of participant motivation and engagement with daily computerized activities. It also allows for a double blind study design. Games from the website Sporcle.com will be used and an online account can be created for each participant. This feature allows the research team to track compliance and progress on the assigned computer games. This approach has been successfully used as a rigorous control condition for computerized cognitive training studies in schizophrenia (e.g., Fisher et al., 2009, 2010; Keefe et al., 2011) and is currently being employed in Dr. Seal's (consultant) cognitive training study of Veterans with PTSD. The Sporcle.com computer games require low cognitive demand, and based on previous studies, are not anticipated to affect cognitive performance in the proposed training domains.

2a.3.i. Measures. Please see Tables 1 and 2 for a schedule of measure administration.

Measures: Diagnostic and Screening.

Demographics: A brief self-report demographics questionnaire will be administered to obtain information on

participant sex, age, marital status, ethnicity/race, education level, income, employment, and era of service.

AUD, PTSD, Axis-I. The Structured Clinical Interview for DSM-IV (SCID-I; First et al., 1995), will be used in the screening phase to insure that individuals meet diagnostic criteria for current AUD. It will also be used to exclude and refer individuals with active homicidal or suicidal intent or psychosis and to exclude individuals with psychotic disorders and schizophrenia. *The SCID-I for DSM-5 will be incorporated upon its release (www.dsm5.org)*. The Clinician-Administered PTSD Scale (CAPS; Blake et al., 1995), which is currently being modified for DSM-*5* (Weathers et al., 2012; National Center for PTSD), will be used to index history of DSM-*5* defined traumatic event exposure (www.dsm5.org), including most distressing event, time since exposure, and total number of exposures, as well as frequency and severity of total and specific posttraumatic stress symptoms. The CAPS has excellent psychometric properties (Weathers et al., 2001) and will be used to insure that individuals meet diagnostic criteria for PTSD. All diagnostic assessments will be combined with a review of clinical records, information from the primary therapist and/or psychiatrist.

Pre-morbid Intelligence; Reading/Mental Retardation Proxy Screen. The Wechsler Test of Adult Reading (WTAR; Coporation, 2001) will be administered as a measure of pre-morbid intelligence and as a proxy screen for inability to read and mental retardation. The test has excellent internal consistency and temporal stability and is highly correlated with WAIS-III verbal IQ (Wechsler, 2001).

Traumatic Brain Injury (TBI). The 4-item self-report DoD TBI screening tool will be administered to screen for severe TBI and is a modified version of the Brief TBI Screen (Schwab et al., 2007) which assesses for past and current TBI and related symptoms based on the American Congress of Rehabilitative Medicine criteria. Consistent with prior research, endorsement of items 1 and 2 are suggestive of TBI (Terrio et al., 2011).

Dementia Screen. The Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) is a widely-used general cognitive screen to rule out dementia. The MMSE assesses orientation to time and place, and basic attention, language and memory. Participants scoring below 24 will be excluded from participation.

Cognitive Impairment. Mild Cognitive Impairment (at least 1 SD below the mean) in at least one domain of cognitive functioning will be determined using a carefully selected battery of neuropsychological tests to be administered in the screening visit (See Table 1, tests denoted with *). A commonly used Global Deficit Score (GDS) approach (see Carey et al., 1994) will be used to summarize neuropsychological screening tests. First, Domain Deficit Scores (DDS) will be computed for each of the 4 domains in Table 1 by converting standard, normed scores (T scores) on the domain measure to deficit scores ranging from 0 (no impairment; $T \geq 40$) to 5 (severe impairment; $T \leq 19$). The GDS is calculated by taking the average of the summed DDS and thus, reflects the number and severity of impaired performances throughout the test battery, with less weight given to performances within normal limits (GDS ≥ .25).

Measures: Stage 1- Feasibility. Usability and Acceptability Measures *(*see also 2a.3.h Stage 1).

To examine acceptability and usability of the cognitive training program and computer game control we will collect qualitative and quantitative data using usability testing procedures, questionnaires, and semi-structured participant interviews and focus groups (condition enrollment permitting). This multipronged analytic approach will help improve protocol feasibility and allow for a richer understanding of patient attitudes and beliefs surrounding cognitive training as well the factors that may interfere with training engagement and completion. Overall feasibility will be evaluated though: (1) attrition rates; (2) adherence to training (number of completed trainings); (3) reports and questionnaire ratings of acceptability and usability; (4) usability testing in the Human Computer Interaction Laboratory; (5) semi-structured interviews and moderated focus groups with participants.

Questionnaires. The cognitive training acceptability measure is comprised of a 22-items used by Posit Science to evaluate acceptability for their cognitive training software, and from components of a measure used by Dr. Vinogradov's research team. Items specifically assess user experience and satisfaction with the program, the web-based administration and the training schedule. The Computer System Usability Questionnaire (Lewis, 1995) will be employed to further assess usability. The 19-item CSUQ asks participants to rate the ease of usability, satisfaction, and enjoyability of a computer program.

Measures: Cognitive Functioning. The proposed neuropsychological test battery was carefully selected to assess the cognitive domains targeted for training and incorporates widely-used, standardized, well-validated and reliable measures. To minimize practice effects, alternative test forms will be used for repeated test administrations whenever feasible. The battery (see Table 1) will take approximately 2 hours, including allowances for breaks. Neuropsychological test data will be scored based on standardized age and, when available, educational and other demographic norms, and transformed into *z* scores for consistency. Specifically, raw scores on individual tests will be converted into *z* scores based on tables mapping normative

population data to optimal Gaussian distributions. A single Global Cognition Score (GCS) will be calculated to assess the impact of training on global cognitive functioning so as to reduce the variability and number of multiple comparisons. Specifically, *z* scores for tests within each domain will be summed and averaged to yield 4 Cognitive Domain Scores which will be summed to produce a single GCS (Strauss et al., 2006).

Basic Attention; Cognitive Bias. The WAIS-IV (Wechsler, 2008) Processing Speed Index subtests will be employed: (1) Digit-Symbol Coding – participants copy symbols paired with numbers (based on a legend) as quickly as possible in a 2 minute time span ; (2) Symbol Search – participants must determine whether one of two target symbols match any of the symbols in a search group, as many times as possible in a 2 minute time span. On the Trail Making Test (TMT) – Part A (Reitan, 1955) participants are asked to draw lines connecting consecutively numbered circles on a work sheet as quickly as possible. Performance is based on time to complete the task. Computerized Approach Avoidance Tasks (Wiers et al., 2011; Amir et al., 2012) that measure the extent to which participants approach and avoid alcohol-related and threatening stimuli will be used to assess cognitive and attentional biases observed in AUD and PTSD.

Verbal and Visual Learning and Memory. The Revised Hopkins Verbal Learning Test (HVLT-R; Brandt & Benedict, 2001) assesses learning and memory for a 12-word list (organized into three semantic categories) immediately after the list is read (trial 1), cumulatively across trials (sum trials 1-3) and after a delay (free recall after 25 minutes). The Brief Visual Memory Test Revised (BVMT-R; Benedict, 1997), asks participants to learn and reproduce 6 abstract designs over 3 learning trials and to reproduce them again after a 25 minute delay.

Working Memory. The Wechsler Adult Intelligence Scale-IV (WAIS-IV; Wechsler, 2008) Working Memory Index subtests will be employed: (1) Digit Span – participants are asked to repeat a number sequence, repeat in reverse order and then repeat in a sequential order; (2) Arithmetic – participants are asked to mentally solve arithmetic word problems within a time limit; (3) Letter-Number Sequencing – participants are asked to recall a combination of numbers and letters that they must first numerically and alphabetically sequence.

Impulsivity and Decision Making. The Conners' Continuous Performance Task II (CPT-II; Conners & Staff, 2000) is a computerized task that assesses vigilance and sustained attention. The participant is presented with a stimulus at variable interstimulus event rates and is asked to respond to all stimuli except the "X." Thus they must maintain a continuous response set (sustained attention) and inhibit responding when a specific target is presented. The Color-Word Interference Test is included in the DKEFS tests (DKEFS; Delis, Kaplan, & Kramer, 2001) and is a variant of the Stroop procedure. Participants are asked to name the ink color (e.g., blue) in which different color words (e.g., red) are printed and thus the test captures ability to inhibit an overlearned response. The Iowa Gambling Task (IGT; Bechara et al., 1994) is computerized and participants select from among 4 decks of cards that vary in monetary reward and punishment (i.e., risky "bad" decks that result in infrequent but large losses and "good" decks that result in gradual monetary gain over repeated trials). The IGT will be used to assess decision-making. The Delay Discounting Task (Richards et al., 1999) asks participants to choose between a hypothetical *smaller* amount of money that could be received immediately, or a larger delayed reward to be received after different delay periods. Indifference points are calculated for each delay and fit with a hyperbolic function to yield a *k* value; larger *k* reflects steeper discounting of future rewards.

Mental Flexibility. On TMT Part B (Reitan, 1955) participants are asked to connect consecutively numbered and lettered circles, alternating between letters and numbers, as quickly as possible (speeded set-shifting). The Wisconsin Card Sorting Test – computer version 4 Research Edition (WCST; Heaton et al., 1993) uses stimulus cards to assess set-shifting, an index of cognitive flexibility. Participants must match a stimulus card to the appropriate card deck based on shape designs and rules that shift throughout the task. The Tower Test is included in the Delis-Kaplan Executive Function System Tests (DKEFS; Delis et al., 2001) and participants are tasked with moving five disks across three pegs to construct a target tower in the fewest number of moves possible. The Tower test will be used to assess planning and procedural problem solving.

Table 1. Neuropsychological Assessment Battery * indicates screening measure

Domain	Test	Specific Functions
Basic Attention and Cognitive Bias	Trail Making Test Part A* WAIS-IV Symbol Search WAIS-IV Digit Symbol Approach-Avoidance Task	Visuomotor Attention and Processing Speed Attentional and Cognitive Biases

Verbal and Visual Learning & Memory Working Memory	Brief Visual Memory Test-R Hopkins Verbal Learning Test–R* WAIS-IV Arithmetic WAIV-IV Digit Span WAIS-IV Letter Numb Sequencing*	Visuospatial learning and recall memory Auditory learning and recall memory Abstract Reasoning, Mental Calculation Mental Tracking, Organization, Sequencing Mental Reorganization; Sequencing
Impulsivity and Decision Making	Delis-Kaplan Color-Word Stroop Test Continuous Performance Task* Iowa Gambling Task Delay Discounting Task	Inhibition of an over-learned response Sustained Attention, Vigilance, Inhibition Decision-Making, Risk-taking Decision-Making, Reward Processing
Mental Flexibility	Wisconsin Card Sorting Task Delis-Kaplan Tower Task Trail Making Test Part B*	Rule-Learning, Set-Shifting Planning, Rule-Learning Speeded Set-Shifting

Measures: Alcohol Use

Alcohol Use. The Time-Line Follow-Back (TLFB) interview provides a calendar-guide of a targeted time period to help participants retrospectively record the number of standard drinks consumed on each day. The TLFB procedure has demonstrated good reliability and validity in past work across diverse samples (Sobell & Sobell, 1992) and data will be used to calculate the primary drinking outcome variable, average drinks per drinking day (the number of drinks consumed divided by the number of drinking days). The TLFB will be administered in an interview format at each study visit.

Breath Alcohol Concentration (BrAC). The *Intoximeter Alco-Sensor IV* (Intoximeters Inc.) instrument will be used to measure BrAC at each visit to ensure that subjects are not acutely intoxicated.

Measures: Functional Status and PTSD Symptom Severity.

Drug User Quality of Life Scale (DUQLS; Brogly et al., 2003). The DUQLS is a culturally relevant tool for assessing quality of life and satisfaction among individuals with SUD. Participants are also asked to classify each of the 22 life areas (including SUD treatment) as "important" or "unimportant" to them. Reponses on the DUQLS can be summed to generate an overall quality of life score as well as sub-scores that reflect quality of life in life areas that are important and unimportant to the participant.

Psychosocial Functioning: The 80-item Inventory of Psychosocial Functioning (IPF; Marx et al., 2009), was developed among Veterans to assess level of functional impairment. The IPF includes self-report and behavioral indices that assess current psychosocial functioning across 7 domains. Domain scores are summed to yield a total score for psychosocial functioning.

PTSD Symptoms. The PTSD Checklist – Military Version (PCL-M; Weathers et al., 1993) is comprised of 17 items that correspond to the 17 DSM-IV (APA, 2000) symptoms of PTSD. The PCL-M provides an index of global PTSD symptom severity and will be administered throughout the study. The 20-item PCL-M for DSM-*5* is being piloted (Weathers et al., 2012; National Center for PTSD) and will be incorporated upon its release.

Measures: Potential Covariates and Secondary Measures. Potential covariates will be included in an initial analytic model for Stage 2 if deemed necessary (e.g., not evenly stratified through randomization).

Non-Alcohol SUD Diagnoses and Use. Non-alcohol SUD and other Axis-I psychiatric disorders will be determined at baseline with the SCID-I (First et al., 1995), modified for DSM-*5*. TLFB interview procedures (see above; Sobell & Sobell, 1992) will be used to assess patterns of non-alcohol substance use.

Attention Deficit Hyperactivity Disorder. Conner's Adult ADHD Diagnostic Interview for DSM-IV (CAADID; Epstein et al., 2001) will be administered at baseline to specifically asses for ADHD.

Alcohol Dependence Severity. The 10-item Alcohol Use Disorder Identification Test (AUDIT; Saunders et al.,1993) will be administered at each visit to assess alcohol dependence and harmful and hazardous drinking.

Prescription Medication Use: All prescription medications will be documented at baseline. Changes in prescription medication use and dose will be tracked using self-report and the VA electronic medical record.

Training adherence and performance. Number of hours completed and aggregated performance indices (i.e., training effort and dose) will be recorded directly from the computer programs each training week.

AUD and PTSD Treatment: Information on past and concurrent AUD and PTSD treatment will be gathered at each study visit using the Psychosocial Treatment Interview (PTI) (Steketee et al., 1997).

Depression and Anxiety: General levels of depression and anxiety will be measured at baseline and each study week with the 64-item Inventory of Depression and Anxiety Symptoms (IDAS; Watson et al., 2007).

Table 2. Overview of assessments to be administered

Clinical Assessments and Procedures	Phone Screen	Screening Visit	Baseline Assessment	Each Study Week	Week 3	Week 6 Post-Training	*3 or 6* Month Follow up
Inclusion/Exclusion							
Study Explanation	X						
Demographic Information	X	X					
SCID-I – AUD		X					
CAPS – PTSD Interview		X					
Cognitive Screening-Table 1*		X					
WTAR – Premorbid IQ Proxy		X					
MMSE – Dementia Screen		X					
DoD Severe TBI Screen		X					
Outcomes							
(S1) Acceptability/Usability Measures and Testing			X (orientation)		X	X	
(S1) Interviews and/or Moderated Focus Groups					X	X	
Neuropsych Assessment			X			X	X
TLFB – Alcohol Consumption			X	X		X	X
DUQLS; IPF - Functional			X			X	X
PCL – M – PTSD symptoms			X	X		X	X
Potential Covariates, Secondary Measures							
TLFB - non-alcohol sub use				X		X	X
SCID-I (Axis 1 disorders)			X				
CAADID – ADHD			X				
AUDIT – AUD Severity			X	X		X	X
Training Adherence				X			
IDAS – Depression/Anxiety			X	X		X	X
PTI - Past/Current Treatment	X		X	X		X	X
Prescription Medication	X		X	X		X	X
Other							
Collateral history from medical record/outpatient SUD treatment team as necessary							
Study Informed Consent		X					
Randomization Checklist			X				
Training Check-in Meetings				X			
Breath Alcohol Concentration		X	X	X		X	X

2a.3.j. Planned Data Analysis.

Missing Data. All laboratory-based measures will be reviewed for completeness immediately following collection, prior to the participant's dismissal. Despite our intensive protocol to limit participant attrition, we do expect missing data over the course of this study (i.e., 30%) and have adjusted our recruiting sample accordingly. To minimize the impact of missing data from incomplete protocols, we will use model-based multiple imputation procedures appropriate for longitudinal research described by Schafer and Graham (2002) and conduct analyses to evaluate the sensitivity of the results to model assumptions (Little & Rubin, 1987).

Power Analysis. Analyses are powered based on a sample size that accounts for 30% attrition in both study stages (i.e., Stage 1, n = 14; Stage 2; n = *90*). For Stage 1, the primary aim is to examine usability, acceptability and feasibility of both the cognitive training and the computer-game control. The proposed recruitment sample size (n = 20; 10 training, 10 control), which allows for up to 30% attrition, should be adequate given that previous studies have found that 3-7 test users is sufficient to identify the majority of usability problems (Nielsen & Landauer, 1993). This sample size will also allow us to conduct a sufficient number of in-depth multi-modal assessments to identify acceptability concerns. For Stage 2, we conducted a

power analysis to determine the needed sample size to analyze the *primary* hypothesis under Aim 2 while balancing Type I and Type II error rates. Three sources of information were considered: (1) Existing empirical work involving cognitive training among AUD populations has established medium to large effect sizes for cognitive outcomes (partial η^2 = .1, Rupp et al., 2012; Cohen's *d* = .42, .64, Goldstein et al., 2005; partial η^2 = .27, Houben et al., 2011a), (2) Dr. Vinogradov observed an effect size of *d* = .66 for Global Cognition in her recently completed study among individuals with schizophrenia comparing a cognitive training intervention to a computer-game control condition (both of which will be employed in the proposed study); (3) The magnitude of change in neuropsychological test performance required to detect a clinically significant and meaningful effect (e.g., Temkin et al., 1999). Together, the described considerations led to a sample size recruitment estimate of *128* participants (*64* training, *64* control) for Stage 2, that will allow for up to 30% attrition. Calculations are based on the most conservative test of group mean differences, a 2-tailed independent samples t-test. Accounting for 30% attrition, a final sample size of *90* will provide an estimated power of 80% to detect a medium effect (*d = .60)* of cognitive training at follow-up (that is also within the range of observed effect sizes in other cognitive training studies with AUD) at an alpha level of .05. Given that previous cognitive training studies in AUD samples have reported medium sized effects for alcohol outcomes (partial η^2 = .16; Houben et al., 2011a; partial η^2 = .12; Rupp et al., 2012; partial η^2 = .1; Eberl et al., 2013) and psychological well-being (partial η^2 = .12; Rupp et al., 2012), the proposed sample size should also be adequately powered to test Aim 2 *secondary* hypothesis b (alcohol, PTSD and quality of life outcomes).

The normality and range of data distributions will be examined and appropriate data transformations will be made when necessary. The data will also be screened for violations of assumptions underlying the statistical tests described below and when necessary, models will appropriately account for factors that vary with time across the study (i.e., training adherence). To control for Type-1 error rates cognitive outcomes will be tested using a Global Cognition Score (see 2a.3.i. Measures). Through randomization, we anticipate that the groups will be comparable in terms of demographic characteristics, premorbid intelligence, cognitive impairment, Axis-1 disorders, treatment participation, prescription medication use, training adherence and AUD and PTSD symptom severity. If significant differences exist, as indicated by Chi Square and t-tests, we will statistically adjust for these effects via inclusion as covariates in the analyses. We will conduct both a per protocol analysis on subjects who complete a minimum of 30 hours of training, and an intent-to-treat analysis on all randomized subjects, and report any differences in retention rates between the two conditions. For all models, variation inflation factors and tolerance will be obtained to assess for collinearity concerns. To account for family wise error, alpha will be adjusted in all secondary and exploratory analyses.

Stage 2, Aim 2 Hypotheses 1a – b. Participants who receive cognitive training as compared to those receiving a computer-game control training, will demonstrate at *6* month post-training follow-up: Aim 2 Hypothesis a *(Primary)*: greater improvements in cognitive outcomes (Global Cognition Score); Hypothesis b *(Secondary)*: reduced alcohol consumption (drinks per drinking day) and PTSD symptoms (PCL-M) and improved quality of life outcomes (DUQLS, IPF). In order to test these hypotheses, a series of 5 multiple linear regression tests will be conducted to assess the effect of condition on each primary outcome. Step 1 will include the baseline level of the primary outcome. Condition (intervention, control) will be entered on Step 2. Step 3 will include any necessary covariates (described above in *Planned Data Analyses*) to determine if effects still remain. From this model we will be able to estimate the covariate and baseline adjusted mean changes, and 95%CIs, in global cognition, alcohol use, PTSD and quality of life outcomes *6* months post-training. **Secondary analyses.** Planned secondary analyses will mirror the above description for primary analyses. First, to follow-up the analysis with global cognitive functioning, we will explore the effects of cognitive training on targeted cognitive domains using individual Cognitive Domain Scores as outcomes. Second, although we expect gains observed in the cognitive training group to be sustained throughout the follow-up period (i.e., persistence of neuroplasticity based cognitive training benefits), we will determine whether the Global Cognition Score changed from post-training to follow-up. This statistical approach is more dismantled and therefore more specific, and offers several advantages over repeated measures ANCOVA.

Stage 2, Aim 2a Exploratory Hypothesis. Changes in global cognition will be significantly associated with decreases in alcohol consumption, PTSD symptom severity and increases in quality of life outcomes. Change scores will be computed for the Global Cognition Score, average drinks per drinking day, the PCL-M and the DUQLS and IPF, by computing the difference between follow-up and baseline. Four Pearson correlations will be performed to test associations between composite index change scores for Global Cognition and the 4 recovery outcomes. *Exploratory Mediation and Moderation. We will explore potential mediators (i.e., training adherence and performance) and moderators (i.e., AUD and PTSD severity; Alcohol Use) of the effects of training condition on cognitive outcomes. The MacArthur approach to moderation and mediation analysis (Kraemer et al., 2008) will be employed. These analyses are considered exploratory*

because, although the study is powered to detect main effects, we will have power to detect only very strong interaction and mediating effects.

2a.3.k. Timeline for Primary and Secondary Research Activities (See Table 3).

Primary Research Activities. During the start-up phase (months 1-3) of the proposed work, we will coordinate recruitment procedures with the outpatient SUD treatment program, finalize and purchase assessment and training tools and train study personal in the study protocol. A recruitment goal of *4* eligible participants per month was chosen based on prior experiences of the mentorship team who agreed that the goal was realistic and sufficient to meet study objectives, and to allow adequate time to conduct follow-up assessments. Recruitment for Stage 1 will start month 4 and last for *5* months. The weekly and post-training assessments for Stage 1 will be completed in month *9* and 3 month follow-ups will be completed in month 12. We will reserve time during months 13 and 14 to incorporate feedback from Stage 1 to refine the protocol and optimize feasibility for Stage 2. Stage 2 recruitment will begin at month 1*5* and will last until approximately month *46-47*. Therefore, including start-up and Stage 1, all data should be collected by the *middle of year 5*.

Secondary Research Activities. In addition to the primary research activities outlined above and the training activities outlined below, I will also engage in manuscript writing, grant writing, and dissemination to further bolster my research program. Throughout the proposed award I will publish at least 4 manuscripts with members of my training team (using the existing prospective datasets they have made available to me) that examine cognitive mechanisms in SUD and PTSD. Publications will include the following topic areas: (1) cognitive influences on the relation between PTSD and AUD (Drs. Bonn-Miller, Batki); (2) prospective evaluation of cognitive influences on treatment outcomes in SUD, PTSD and SUD-PTSD (Drs. Bonn-Miller, Trafton, Sox-Harris); (3) contribution of impulsivity and related cognitive processes across addictive behaviors (Dr. Trafton); (4) an integrative review of neurocognitive deficits observed in AUD and PTSD (Drs. Trafton, Vinogradov). These projects will serve to inform cognitive screening procedures for Veterans entering SUD treatment that could be implemented to aid clinicians in treatment planning and delivery. This research in conjunction with initial CDA-2 data will also aid in the development of VA Investigator Initiated Research (IIR) grant. Specifically, beginning in the second half of year 4 I will develop a grant that proposes a larger-scaled randomized controlled clinical trial of mobile-based cognitive training for dually diagnosed SUD patients (e.g., SUD-PTSD). The primary aim of this grant is translational in nature. It will use data collected on malleable cognitive functions identified and therapeutically targeted in the proposed CDA-2, to generalize beyond AUD to other vulnerable SUD populations with complex comorbidities and across different VA treatment programs. In collaboration with operations partners (PERC, Dr. Trafton, SUD-QUERI, Dr. Sox-Harris), this research will also assess implementation and cost factors associated with cognitive training. Year 5 will be dedicated to revision and resubmission of the IIR and dissemination of findings via publications and presentations.

Table 3. Study Timeline.

Primary Activities	Year 1	Year 2	Year 3	Year 4	Year 5
Month	1 3 6 9 12	15 18 21 24	27 30 33 36	39 42 45 48	51 54 60
Start-up	|----|				
Stage 1:					
Baseline	|----|				
Training	|-----|				
Follow-up	|----|				
Incorporate Feedback	|----|				
Stage 2:					
Baseline	|----------|				
Training	|----------|				
Follow-up	|----------|				
Data Analyses				|-----|	
Secondary Activities					
Manuscript Writing	|----------|				
Grant Writing			|----------|		
Dissemination				|----------|	