Assessment and Treatment of Cognitive Functioning Deficits in Veterans with PTSD

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Research Protocol

Title
"Assessment and treatment of cognitive functioning deficits in Veterans with PTSD"

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Specific Aims/Purpose
PTSD is common in Veterans of wartime service eras, particularly those who receive VHA services: Over 500,000 Veterans receive VHA PTSD treatment each year. PTSD is associated with both objective cognitive impairment and subjective (self-reported) cognitive problems. A recent meta-analysis provides strong support for associations between PTSD and worse performance on cognitive tests of verbal learning/memory, attention/working memory, executive functions, and processing speed, language, and visual learning/memory. The effect of PTSD on cognition is often independent of mental health comorbidities or TBI history. Although robust research suggests that evidence-based psychotherapy (EBP) for PTSD results in significant improvement in PTSD symptoms, cognitive impairment is associated with reduced PTSD treatment response. Fortunately, Veterans with comorbid PTSD and TBI can benefit from EBP for PTSD, including standard and modified versions that accommodate cognitive impairment. However, some Veterans continue to experience cognitive problems even after completing evidence-based PTSD treatment. Therefore, the VA needs a rehabilitation intervention to address this clinical service gap.

Our research team (including Drs. Huckans, Twamley, and Storzbach) developed **Compensatory Cognitive Training (CCT).** This manualized intervention teaches methods for managing and compensating for cognitive symptoms, thereby reducing suffering and functional limitations. Many aspects of PTSD can influence cognition (e.g., decreased motivation, avoidance, medication side effects). CCT is promising due to its focus on teaching compensatory strategies regardless of the etiology of cognitive deficits. Our studies have demonstrated CCT efficacy for mild TBI and for schizophrenia. Compared to treatment as usual (TAU), CCT significantly improves learning, memory, executive functioning, and attention/working memory, as well as self-reported cognitive, social, and vocational functioning; use of compensatory strategies; and quality of life (QOL). CCT efficacy is not moderated by depression or PTSD, suggesting that CCT might be effective for treating cognitive impairment and improving functioning in Veterans with PTSD, even if they do not have a history of TBI. To test this, we need to study the efficacy of CCT in Veterans without other conditions (e.g., TBI or severe mental illness) that could confound results.

Aim 1: Evaluate recruitment feasibility and participant acceptability and characteristics in a pilot Randomized Controlled Trial of CCT vs. TAU in Veterans who previously engaged in PTSD treatment and report current cognitive functioning deficits.

Aim 2: Estimate effect sizes to calculate needed sample size for a fully powered RCT of CCT vs. TAU for improving objective and subjective cognitive functioning deficits, mental health, other aspects of functioning, and QOL.

VA Portland IRB
Effective Date: February 2, 2024

Hypotheses: *(1) CCT will be feasible and acceptable to participants in a pilot RCT of CCT versus TAU for Veterans who have previously participated in PTSD treatment and report current cognitive functioning deficits. (2) We will be able to collect adequate feasibility, acceptability, and participant characteristics data to inform a future, fully powered RCT of CCT versus TAU for Veterans with PTSD-related cognitive functioning deficits. (3) Effect size data from this pilot RCT of CCT versus TAU will allow us to estimate effect sizes and needed sample size for a fully powered RCT comparing CCT versus TAU on outcomes including objective and subjective cognitive functioning, mental health symptoms, social functioning, and QOL in Veterans with PTSD-related cognitive functioning deficits.*

Scientific Rationale and Significance

Posttraumatic stress disorder (PTSD) is common among Veterans of all wartime service eras, particularly those who receive VHA services (Harpaz-Rotem & Hoff, 2015). Over 500,000 Veterans each year have received PTSD treatment through the VHA since 2011 (US Department of Veterans Affairs, 2016). PTSD is a mental health disorder resulting from exposure to one or more traumatic events. According to the Diagnostic and Statistical Manual of Mental Disorders fifth edition (DSM-5), PTSD is characterized by symptoms of intrusive re-experiencing of a traumatic event, avoidance of associated stimuli and reminders, alteration in mood and cognitions, and persistent physiological arousal and reactivity which impact functioning and persist for at least one month (APA, 2013). Approximately 50% of women and 60% of men in the US will experience one or more traumatic events in their lifetimes, and an estimated 8,000,000 people in the US meet criteria for PTSD in a given year (NCPTSD, 2015). Up to 20% of Veterans from the Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) service era screen positive for probable PTSD compared to 10-12% from the Gulf War era and around 15% from the Vietnam era (Dohrenwend, 2006; Hoge et al., 2004; Kang et al., 2003; NCPTSD, 2015; Terhakopian et al., 2008).

While research has historically emphasized mental health symptoms of PTSD such as flashbacks, nightmares, avoidance, and hypervigilance, PTSD is also associated with objective and subjective (self-reported) cognitive functioning deficits (Roca & Freeman, 2010). Subjective deficits are not surprising given that concentration difficulties are a core symptom of PTSD (DSM-5, 2013). PTSD symptoms include self-reported cognitive problems such as intrusive memories; inability to recall details of the trauma; hypervigilance or attentional bias toward trauma reminders, threats, or extraneous environmental details; and concentration difficulties including moderating control over trauma-related thoughts (Brewin 2007; Litz et al., 1996).

A recent meta-analysis of cohort studies provides strong support for associations between PTSD and objectively assessed cognitive functioning deficits (Scott et al., 2015). Effect sizes for impairment across cognitive domains were generally of medium magnitude (Cohen, 1988; Borenstein et al., 2009). Effect sizes ranged from *d* values of -,62 (verbal learning), -.59 (speed of information processing), -.50 (attention/working memory), -.46 (verbal memory), -.45 (executive functions), -.43 (language), -.38 (visuospatial functioning), -.32 (visual learning), to -.29 (visual memory). These effects were mediated by PTSD symptom severity for verbal learning but not for attention/working memory or speed of information processing. Even in Veterans with a history of mild traumatic brain injury (TBI), objectively assessed and self-reported cognitive functioning deficits are largely explained by PTSD, and not due to long-term consequences of mild TBI (e.g., Vasterling et al., 2012; O'Neil et al., 2014; Storzbach,* O'Neil,*

et al., 2015 [shared first authorship]). Research confirms the links between PTSD and both functional and structural brain changes related to cognitive functioning (Morey et al., 2012; Shin et al., 2006). While underlying neurobiological mechanisms for associations between PTSD and cognitive impairment need further investigation, some theories have been supported by recent imaging research. For example, PTSD has been associated with biological differences in numerous areas of the brain including the amygdala, hippocampus, dorsolateral and ventromedial regions of the prefrontal cortex, and the cingulate cortex (Brown & Morey, 2012). These regions of the brain are associated with many PTSD-related functions (e.g., emotions, memory, and fear) as well as functions not traditionally associated with PTSD such as episodic memory, affective and cognitive control, processing of ambiguous information, attention, working memory, and decision making.

Cognitive functioning deficits associated with PTSD often interfere with other aspects of functioning and quality of life (QOL; e.g., Pittman et al., 2012; Vasterling & Verfaellie 2009). Wrocklage et al. (2016) report that executive functioning deficits in Veterans with PTSD is associated with poorer occupational functioning; both executive functioning and speed of information processing deficits are associated with poorer physical health-related QOL. Similarly, Gueze et al. (2009) report that PTSD in a Veteran sample is associated with memory deficits which in turn predict impairments in social and occupational functioning. A very recent study (Silverberg et al., 2017) examined relationships among PTSD and depression symptom severity, cognitive functioning, and QOL in Veterans and US Service Members with PTSD. This study found that cognitive functioning was independently associated with QOL (beta = -.204). This relationship was not related to TBI history, though was related to depression.

A robust body of research suggests that evidence-based psychotherapy (EBP) for PTSD results in clinically significant improvement in PTSD symptoms for many individuals with PTSD, including Veterans (Cusack et al., 2016). Some recent research suggests that Veterans with comorbid PTSD and mild to severe TBI can benefit from EBP for PTSD, while other preliminary research suggests that cognitive impairment is associated with reduced PTSD treatment response. Despite reducing PTSD symptoms for many Veterans, it is common for others to have significant PTSD symptoms even after participating in EBP. For example, in some studies, less than half of Veterans receiving EBP for PTSD achieved loss of diagnosis (e.g., not meeting diagnostic criteria on the Clinician Administered PTSD Scale [CAPS] or scoring less than 50 on the PTSD Checklist [PCL]; Yehuda et al., 2014; Schnurr et al., 2015). While some Veterans may see improvement in cognitive functioning after EBP reduces related PTSD symptoms (e.g., re-experiencing, hyperarousal, avoidance, and numbing), others may have engrained cognitive functioning deficits or other residual symptoms such as sleep difficulties that affect cognition (Schnurr et al., 2015, Verfaellie et al., 2015).

Given that PTSD-related cognitive functioning deficits persist for some Veterans even following PTSD treatment, interventions should be developed to effectively treat them. The VA/DoD PTSD Clinical Practice Guideline (CPG, 2010) recommends that if residual symptoms follow EBP, adjunctive therapies targeting individual symptoms should be considered. However, the CPG does not cover any treatments specifically targeting PTSD-related cognitive functioning deficits. Similarly, the National Center for PTSD (NCPTSD) website section on “Assessment and Treatment of PTSD with Co-Occurring Neurocognitive Disorder,” notes that “PTSD commonly co-occurs with neurocognitive disorders (NCD), yet specific assessment techniques and treatments for patients with both diagnoses have not been established” (2015).

Compensatory Cognitive Training (CCT) is a promising intervention for treating cognitive functioning deficits in Veterans. CCT draws from the theoretical literature on compensatory strategy training for other cognitively impaired populations (e.g., Huckans et al., 2013; Twamley et al., 2010; Storzbach et al, 2016). It is a rehabilitation model that aims to teach individuals strategies that allow them to work around cognitive deficits. Consistent with this model and the expert recommendations for civilians and Service members with TBI (Cicerone, 2011), manualized CCT treatment provides training in compensatory attention and learning/memory skills, formal problem-solving strategies applied to daily problems, and the use of external aids such as calendar systems and assistive devices to promote completion of daily tasks (Storzbach et al., 2016). CCT is a promising intervention for PTSD-related cognitive problems due to its focus on teaching and practicing compensatory strategies regardless of the etiology of cognitive functioning deficits. CCT sessions focus on practical and generalizable compensatory strategies such as organizing home and work life and priorities from daily goals and check lists to physical layout changes to facilitate ease of functioning. Veterans also work on implementing a calendar support system, most often through a smart phone or small day planner, to help them use efficient and repeated reminders about activities and behaviors that support their larger goals. Examples include weekly reminders for support groups, social activities, work or school meetings and assignments, and medical appointments. Daily reminders are used for physical activities, family check-ins, meal preparation, pet or childcare, and medications. Stress management strategies such as progressive muscle relaxation or circle breathing, with VA smartphone app support when appropriate, are also incorporated into daily and weekly schedules, which supports common mental health treatment goals. Specific memory, learning, executive functioning, processing speed, working memory, attention, and concentration strategies are also taught as part of this intervention, with specific examples tailored to each Veteran's goals and unique circumstances in ways that are relevant to everyday functioning (e.g., returning to school, attending multiple medical appointments, overcoming challenges at work, etc.). The strategies used in CCT are all taught and rehearsed in sessions. CCT is applicable to many scenarios involving cognitive functioning deficits associated with mental health and chronic stress, and helpful for Veterans who are managing common transitions (e.g., job changes, returning to school, managing conflicting family demands). This pragmatic treatment focused on improving the ability to compensate for cognitive deficits and improve functioning and QOL is therefore very likely to be applicable to individuals with a range of mental health diagnoses including PTSD.

Although not yet formally studied, it is likely that Veterans with PTSD will benefit from CCT even if they do not have a history of TBI. Our team's recent trial of CCT for Veterans with a history of mild TBI provides relevant preliminary data to support this hypothesis. Post hoc analyses of these CCT clinical trial data and examined whether mental health, including PTSD, depression, and substance dependence, moderated the efficacy of CCT for Veterans with a history of mild TBI. None of the mental health factors moderated CCT efficacy in Veterans with a history of mild TBI, suggesting that a further investigation of CCT for Veterans with PTSD, but without a history of TBI, is appropriate (Pagulayan,* O'Neil,* Storzbach, et al., in press [*shared first authorship]). Currently, a small trial of CCT in Veterans with comorbid PTSD and TBI is ongoing (Jak, 2015), though results of this trial are not yet available. Finally, Walter et al. (2015) examined the impact of PTSD symptoms on CCT effectiveness for OEF/OIF Veterans with mild to moderate TBI history who received supported employment services. The presence of PTSD did not diminish improvement associated with CCT. No current research is examining the effectiveness of CCT for Veterans who have PTSD but who do not have comorbid TBI history.

Because recent research has confirmed that cognitive functioning deficits are present for Veterans who have PTSD but do not have a history of TBI, it is likely that these Veterans will also benefit from an intervention designed to target cognitive functioning deficits, such as CCT. CCT emphasizes the cognitive domains most impacted by PTSD (Scott et al., 2015), and therefore the intervention is well-suited to this population.

Summary: We know that many Veterans experience cognitive functioning deficits associated with PTSD and that, in some Veterans, these persist after PTSD treatment (including EBP). CCT is a promising treatment for mild TBI that can be tailored to Veterans with PTSD. We need to pilot test CCT to determine the feasibility and appropriateness of future research on its effectiveness for reducing cognitive functioning deficits and improving compensatory strategy use in Veterans with PTSD but without TBI. The central hypothesis is that though PTSD treatment will reduce cognitive functioning deficits for some Veterans with PTSD, others will benefit from CCT to address residual cognitive functioning deficits.

Preliminary Studies

Cognitive functioning, mild TBI, and PTSD in Veterans: Dr. O'Neil's research focus derives from clinical neuropsychology practice, in which she assesses and treats Veterans who have PTSD and associated cognitive functioning deficits. Recently completed projects include a VA-funded RCT of CCT for Veterans with mild TBI (Storzbach, Twamley, et al., 2016), a VA-funded RCT of behavioral activation efficacy for PTSD symptom reduction (Storzbach et al., in progress), and a VA-funded study of the affects blast exposure on cognitive outcomes (Storzbach,* O'Neil,* et al., 2015 [shared first authorship]; O'Neil et al., 2016; Callahan et al., 2016; and 2 additional manuscripts in progress). The blast exposure study demonstrated that, though blast exposure was a stronger predictor of cognitive deficits than mild TBI, PTSD symptoms mediated this relationship. This project solidified Dr. O'Neil's focus on PTSD as a relatively unstudied driver of cognitive impairment. The CCT for TBI study provided preliminary support for CCT intervention efficacy for cognitive symptom reduction in Veterans with mild TBI history, and Dr. O'Neil co-led a follow-up paper on mental health moderators of CCT efficacy with Drs. Twamley and Pagulayan, recently published in Archives of Physical Medicine and Rehabilitation. This paper shows that **neither PTSD symptom severity nor PTSD diagnosis moderates the efficacy of CCT for Veterans with TBI history,** suggesting that investigating whether it improves cognitive functioning in Veterans with PTSD but without TBI history is an appropriate next step to advance VA rehabilitation research related to PTSD.

Research Design and Methods

Overview: CCT will be pilot tested with Veterans who have residual cognitive functioning deficits following PTSD treatment to determine the effectiveness of this treatment for reducing cognitive functioning deficits associated with PTSD. These Veterans will be either identified in Dr. O'Neil's concurrent CDA study assessing cognitive functioning in Veterans completing EBPs for PTSD, referred by mental health providers if they received PTSD treatment in the past and are reporting ongoing cognitive functioning deficits, or through the VA CDW, if needed.

Aim 1: Evaluate recruitment feasibility and participant acceptability and characteristics in a pilot RCT of CCT vs. TAU in Veterans who previously engaged in PTSD treatment and report current cognitive functioning deficits. **Aim 2**: Estimate effect sizes to calculate needed sample size for a fully powered RCT of CCT vs. TAU for improving objective and subjective cognitive functioning deficits, mental health, other aspects of functioning, and QOL.

Study Design: The proposed study is a single site, pilot RCT comparing 10-session CCT (one session per week) to 10 weeks of TAU as the control condition.

Intervention: TAU will consist of routine, weekly mental health psychotherapy as all participants must have a referring mental health provider to be eligible for this pilot RCT. The CCT rehabilitation model aims to teach individuals strategies that allow them to work around cognitive deficits. CCT provides training in compensatory attention and learning/memory skills, formal problem-solving strategies applied to daily problems, and the use of external aids, such as calendar systems and assistive devices to promote completion of daily tasks (Storzbach et al., 2016). CCT sessions consists of interactive didactic information and discussion, and activities that introduce a variety of cognitive strategies and external aids. Participants are given a copy of the treatment manual and a paper calendar or day planner if requested, or they may request training on a smartphone or electronic calendar system instead. They will receive extensive graduated training in and practice with their chosen calendar system across sessions with a focus on how the day planners can facilitate the use of compensatory strategies taught each week. Dr. O'Neil will supervise the CCT groups run by the study coordinator, co-facilitating early groups as needed for training purposes. They have an ongoing relationship with local psychology doctoral programs which may provide clinical trainees who may provide supervised group facilitation. The current CCT Treatment Manual (Twamley, Huckans, et al., 2016) is included as an Appendix, though aspects of structure and content will be changed before this pilot RCT for PTSD to tailor the intervention to PTSD rather than TBI. We have successfully tailored CCT to other similar Veteran populations in the past, and we expect to be able to refine it for Veterans with PTSD prior to CDA initiation. We have also had success training a variety of master's level research associates and providers to administer the intervention, and similar training and fidelity monitoring protocols (e.g., recorded sessions, 20% random fidelity checks) previously utilized by Drs. Storzbach, Twamley, and Huckans will be implemented in this proposed efficacy study. The following table outlines the CCT structure and content.

Table of CCT for PTSD Session Content

Session	Major Concepts	Examples of Strategies	Session Activities	Home Exercise
1	Intro and PTSD/cognitive functioning psychoeducation	Creating a "home" for important items	Day planner use	Finding a home for the day planner
2	Managing physical symptoms associated with PTSD	Strategies for dealing with sleep problems	Progressive Muscle Relaxation, Circle Breathing	Practice PMR 2 times
3	Organization and prospective memory Part I	Time management	Scheduling and concrete goal setting	Practice using the calendar
4	Organization and prospective memory Part II	Weekly planning session	Enter lists and activities into the calendar	Follow through with planning session
5	Attention and concentration	Paying attention during meetings and conversations	Practicing paying attention during conversations	Active listening once a day
6	Learning and memory Part I	Internal memory strategies	Practice chunking	Practice using a strategy everyday
7	Learning and memory Part II	Over-learning and practice effects	Scheduling strategies in planner	Practice using a strategy everyday
8	Planning and goal setting	Goal setting	Planning an important goal	Practice planning a goal
9	Problem-solving and cognitive flexibility	Self-monitoring and tracking behavior	6-step problem-solving method	Practice problem-solving with 2 life goals
10	Skill integration and review	Review, practice, goals, and planning for the future	How to maintain skills and apply them to goals	Provided with additional PTSD-related resources

Feasibility and Acceptability: A goal of pilot studies is to assess feasibility of proposed methods for a larger trial (e.g., recruitment, retention, resource capacity, and data and personnel management). We will examine the feasibility of recruiting and retaining Veterans with recent history of PTSD treatment (past year) and current cognitive functioning deficits for a CCT for PTSD RCT; establish study protocols to ensure adequate recruitment, intervention delivery, and

intervention fidelity; and maximize participant retention. Detailed records on recruitment, session attendance, and homework completion will be kept throughout the intervention. Consistent with Consolidated Standards of Reporting Trials (CONSORT) guidelines, we will obtain data to determine (1) the number of participants who reported moderate or greater symptom ratings, or who have impairments in one or more cognitive domain, from the baseline assessment; (2) the number of participants referred to the study, (3) the number of participants screened by research staff for study eligibility, and (4) the number enrolled in and completing all aspects of the study including treatment sessions and assessments. We will ascertain reasons for unsuccessful recruitment, ineligibility, and unsuccessful enrollment of eligible Veterans. In addition, we will collect data on the intensity of outreach needed to recruit and enroll participants (e.g., number of phone calls required before Veterans complete eligibility screening, number of "no shows" for eligibility screening appointments) and length of time between initial recruitment attempt, eligibility screening, and completion of the pre-intervention assessment. Participant Retention will be measured by the proportion of participants who complete follow-up assessments within two weeks of the target date. Treatment satisfaction will be assessed by the Client Satisfaction Questionnaire (CSQ8).

Functional and Clinical Variables: We will use similar assessment procedures as in the Aim 1 study to assess cognitive and functional domains most strongly associated with PTSD (details listed in the table below). We will examine sleep and mental health symptoms (including PTSD and depression) not directly targeted by CCT to examine comparability to TAU. Assessments will take approximately 1.5 hours and will occur at baseline, post-treatment, and 6-month follow-up for both groups.

Measure	Construct Assessed
Objective Cognitive Functioning (Neuropsychological Tests)	
Test of Premorbid Functioning (ToPF)	Verbal abilities; estimate of premorbid cognitive functioning
California Verbal Learning Test (CVLT-II; Delis et al., 2000)	Verbal learning and memory, forced choice validity
Wechsler Adult Intelligence Scale (WAIS-IV) Digit Span & Coding subtests (Wechsler, 2008)	Attention, working memory, processing speed, reliable digit span validity
Controlled Oral Word Association Test (Benton, Hamsher, & Sivan, 1983)	Word generation, verbal fluency, executive functioning
Halstead Reitan Trailmaking Test (Trails A & B; Reitan & Wolfson, 1985)	Visual tracking, processing speed, executive functioning
Medical symptom Validity Test (MSVT)	Validity
Functional Outcomes (Patient-Reported)	
World Health Organization Disability Assessment scale (WHODAS 2.0)	QOL, global functioning
Neuro-QOL Cognitive Scale	Cognitive functioning and QOL
Neuro-QOL Ability to participate in Social Roles and Activities Scale	Social functioning and QOL
Neuro-QOL Sleep Scale	Sleep-related functioning and QOL
Memory Compensation Questionnaire (MCQ; de Frias & Dixon, 2005)	Compensatory cognitive strategy use
Portland Cognitive Strategies Scale 2.0 (PCSS)	Compensatory cognitive strategy use
Clinical Outcomes (Patient-Reported)	
Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 2006)	Mental health diagnoses
PTSD Checklist (PCL-5; Weathers et al., 2013)	PTSD symptoms and severity
Patient Health Questionnaire (PHQ-9; Spitzer, Kroenke, & Williams, 1999)	MDD symptoms and severity
Prospective-Retrospective Memory Questionnaire (PRMQ; Crawford et al. 2006)	Cognitive symptoms
Multiple Sclerosis Neuropsychological Screening Questionnaire – Patient Version (MSNQ; Venedict et al. 2003)	Cognitive symptoms

All assessments will be administered by the trained study coordinator/assessors supervised by Dr. O'Neil, who is a licensed, credentialed, and privileged VA neuropsychologist.

Randomization and Blinding**:** All eligible participants will be randomized to either the CCT or TAU group. Randomization tables will be prepared by the study statistician at the beginning of the study and assignments to CCT or TAU will be based on the randomization table. New participants will be allocated to the current group awaiting randomization. Once group membership reaches 6 participants, the group will be randomized by the statistician. We will employ a system of adaptive randomization, weighted to achieve the desired proportion of participants in each condition, managed by the statistician. Randomization will be implemented by the study coordinator in coordination with the statistician who will monitor randomization procedures. Because of the small sample size and number of study personnel in this pilot RCT, it might not be feasible to blind the assessor to participant group status if the assessor is also co-facilitating CCT groups with Dr. O'Neil, though this type of blinding will be implemented if possible.

Data Analysis: Rates of recruitment, retention, and participation will be calculated, and we will compare participant characteristics at baseline by group (CCT vs. TAU). We will conduct intent-to-treat analyses to compare change from baseline to 3-month follow-up within and between groups.

Study Feasibility Analyses: Descriptive statistics will characterize the feasibility of recruiting and retaining Veterans. Recruitment will be deemed feasible if we successfully screen for eligibility 50% of Veterans referred to the study and enroll 75% of screened Veterans who meet all study inclusion criteria. Retention will be deemed successful if we achieve 80% completion for post-treatment assessments. Chi-square tests of association for categorical variables and t-tests for continuous variables will compare demographic and clinical characteristics of successfully versus unsuccessfully recruited and retained Veterans to identify characteristics of participants who may require more intensive recruitment or retention efforts in a future trial.

Clinical and Functional Outcome Analyses: An additional goal of clinical and functional outcome data from this pilot RCT is to obtain effect size estimates to prepare for a future fully powered RCT. Because estimating effect sizes in small pilots is fraught with limitations and should not be used as a sole estimate (e.g., Kraemer et al., 2006), we will compare obtained effect sizes to those obtained for participants with PTSD in our CCT for mild TBI trial. We are not relying on the TBI data alone, however, because of the potentially significant differences in Veterans who do and do not have a history of TBI. Therefore, though we will conduct multivariate analyses of pilot data and examine the statistical significance of within and between group differences, we will focus on obtaining effect size estimates to prepare for a future trial. Because of the small sample size, we will examine data for trends to plan for future analyses in a fully powered RCT. To evaluate the proportion of Veterans with early discharges from CCT, we will conduct mixed models for binary outcomes. We will plan for an underpowered pilot trial, though will use the obtained effect sizes to estimate statistical power and needed sample size for the fully powered RCT RR&D Merit proposal in year 4 of the CDA. We will also use appropriate assumptions for planned statistical tests when calculating estimated power.

In this pilot study, we will first examine descriptive statistics, and conduct tests of normality and homogeneity of variance for variables included in repeated measures analyses. We will examine missing data for all variables and dropout rates in order to plan for a future RCT, though will not conduct multiple imputation or other missing data techniques for this pilot study. We will, however, conduct intent to treat analyses, analyzing data from all randomized participants assigned to CCT versus TAU groups, rather than only including completers. Primary outcome analyses will be multilevel models to compare the change over time in cognitive, mental health, functioning, and QOL outcomes for Veterans in the CCT versus TAU groups. If the sample size is too small to run multilevel models, we will run alternative methods such ANOVAs which are more feasible with smaller samples. We will examine how much symptoms change, comparing changes across groups, and also examine clinically significant change in self-reported functional and clinical outcomes. We will compare the change in proportions of Veterans who fall within in "clinically significant impairment" ranges on objective cognitive performance measures before and after CCT versus TAU, characterizing cognitive functioning deficits according to cognitive domains. Because of the small sample size in this pilot RCT, these analyses will rely heavily on descriptive statistics including identifying individuals who score within clinically impaired ranges on objective testing, and who score above clinical cutoffs on self-report measures. Multilevel models or repeated measures analysis of covariance (ANCOVA) models will examine potential moderators including validity tests, service connection status and percent, number of sessions attended, comorbid mental health diagnosis such as PTSD, and demographic variables.

Study Population and Subject Identification/Recruitment

Study setting, sample size, and recruitment feasibility: The proposed study is conducted at a single site. We propose to enroll at least 36, and up to 48, total Veterans in this pilot RCT. Because our primary purposes are to examine feasibility of this clinic-based research and acceptability to Veterans with PTSD and estimate effect sizes for a future fully powered RCT, achieving adequate statistical power is not a primary concern of this pilot clinical trial. Results from this pilot RCT with a sample size of 36 to 48, combined with comparisons to similar studies of CCT with other Veteran groups (e.g., those with mild TBI history), will provide adequate information on expected effect size to allow for estimations of statistical power for a future RR&D Merit proposal of a fully powered RCT. VHAPORHCS Mental Health and PTSD clinics will serve as primary sites for study recruitment, assessment, and intervention activities. We will work with the Public Affairs Office to post IRB approved study flyers in VHAPORHCS Mental Health and PTSD clinics and nearby elevators as well as the main hospital. The flyers provide information about the study and will help notify Veterans of the opportunity to participate in this study. Eligibility and recruitment procedures used to identify Veterans who report residual cognitive functioning deficits following recent (past year) treatment for PTSD at the Portland VA will be used to recruit Veterans for this pilot trial. Veterans who have participated in PTSD treatment and report cognitive functioning deficits on the Neurobehavioral Symptom Inventory (NSI; moderate cognitive symptoms or greater on any cognitive functioning item), will be recruited from the clinics.

CDW: If needed to achieve recruitment goals, we will also access the VA's Corporate Data Warehouse (CDW) and use ICD-10 codes to identify Veterans with recent (past year) Portland VA mental health or PTSD clinic treatment for PTSD. NSI data is also available for some Veterans in CPRS and Veterans with elevated NSI scores or neuropsychological evaluations

will be prioritized for recruitment. The CDW will be used to identify potentially eligible Veterans. The Veterans' clinicians will be contacted to ask them if they would like to refer these identified Veterans to the study. If the clinician wants to refer a Veteran to the study, this will be documented and the IRB approved recruitment procedures for a referred Veteran will then be followed.

Enrollment and Assessment Procedures: Prior to enrollment, interested Veterans will be pre-screened. The study coordinator will conduct a medical record review to document cognitive symptoms, medical and psychiatric history, and recent treatments and medications. The Neurobehavioral Symptom Inventory (NSI) will be used as a screening tool to determine the presence of moderate or greater cognitive symptoms for eligibility purposes. A brief phone interview will ensure that Veterans are interested in participating and meet eligibility criteria. All participants will be screened to ensure their ability to comprehend study procedures, risks and benefits. We anticipate that up to 500 Veterans will need to be screened in order to achieve the desired sample size of 36-48 Veteran participants in the study. Veterans will be provided the opportunity to have the informed consent materials mailed to them. After the Veteran receives the informed consent materials, a trained study team member will call the Veteran to go through the informed consent procedures and answer any questions. If the Veteran chooses to participate, he or she will sign the informed consent documents and mail them back to Dr. O'Neil using a pre-addressed and stamped envelope. The study assessment will only be scheduled after the hard copy informed consent is received back from the Veteran. Following determination of eligibility, provision of informed consent, and enrollment into the pilot trial, Veterans will initiate the pilot RCT assessments, and, when assigned to the CCT condition, the 10-week CCT group intervention (weeks 2-11). Cognitive assessments and symptom questionnaires will be completed at baseline, post-treatment (approximately 3-months following baseline), and follow-up (6-months following baseline). Veterans will have the option to complete all study activities, including the 10-week CCT intervention and the 3 cognitive assessments via the VA's telehealth system, VA Video Connect (VVC), or via telephone.

If a Veteran chooses to complete intervention activities via VVC or telephone, a study team member will mail the Veteran the CCT session materials. If a Veteran chooses to complete the intervention activities via VVC, Dr. O'Neil or another trained, IRB-approved study team member will explain how VVC works and ensure that the Veteran has the appropriate technology and accommodations to ensure VVC will work (i.e., internet connected device with video chat capabilities, internet connection, private space to engage in the intervention). A study team member will schedule intervention sessions with the Veteran and then the Veteran a link for VVC through Virtual Care Manager. If a Veteran chooses to complete intervention activities via VVC or telephone, Dr. O'Neil or another trained, IRB-approved study team member will conduct the intervention via VVC or telephone. If a Veteran chooses to complete assessments via VVC or telephone, a study team member will administer all cognitive tests over the phone by reading the instructions and questions to the Veteran and recording their response. All responses will be recorded directly into electronic files maintained in the IRB-approved VA folders behind the VA firewall. No hard copy or other electronic files will have any study data. All assessment activities can be completed via VVC or telephone with the exception of the Halstead Reitan Trailmaking Test parts A and B and the Wechsler Adult Intelligence Scale Coding subtest. If a Veteran chooses to complete an assessment via VVC or telephone these tests will not be administered.

Participant retention/ Dropout Minimization: Retention activities will include offering the option to complete study activities via VVC or telephone, inviting participants who discontinue treatment

to complete follow-up assessments, advance participant reminders of upcoming assessments, scheduling assessments near the target date at times that are convenient for participants, providing reminder calls 1-3 days prior to the scheduled assessment, and promptly rescheduling missed assessment appointments. We will attempt to retain all enrolled Veterans in the study, regardless of ongoing participation in CCT or other interventions as part of TAU. In our prior research, all Veterans who initiated CCT completed the intervention. For Veterans who discontinue treatment and who express discomfort returning to the clinic to complete follow-up assessments, accommodations will be made to ensure Veterans have the opportunity to continue study participation (e.g., assessment completion via VVC or telephone or at other VAPORHCS locations). We will ensure that participants are appropriately reimbursed for time and travel, paying participants $50 for each assessment. Recent trials of CCT in VA clinics conducted by Drs. Storzbach, Twamley, and O'Neil have exceeded 90% retention.

Inclusion/Exclusion Criteria

Participants will be at least 36 (and up to 48) Veterans weighted with more CCT participants (approximately 4-5 CCT groups with 6 Veterans each) than controls (12-18 TAU participants, grouped for randomization piloting purposes into 6-Veteran participants in each of 2 groups). Veterans of all genders, races, and ethnicities will be eligible for this study. We have estimated enrollment for gender, race, and ethnicity based on the recent CCT for mild TBI study, assuming similar demographic proportions. Eligibility will be established by current Mental Health or PTSD Clinic provider and CPRS chart review and will be confirmed by the Veteran during the initial phone call. Eligible Veterans (1) must meet DSM-5 criteria for PTSD based on PTSD or Mental Health Clinic intake assessment or PTSD diagnosis at most recent Mental Health/PTSD clinic visit if intake was completed over 6 months prior to study participation; (2) are patients in the PTSD specialty clinic or Mental Health clinic with a current mental health provider who is willing to provide TAU if randomized as such; (3) prior EBP treatment within the past 2 years confirmed by patients, their current Mental Health or PTSD clinic provider, and a review of CPRS records; (4) do not have a history of TBI of any severity; (5) are able to provide informed consent; (6) are English speaking; (7) are able to travel to the clinics for appointments; (8) do not have auditory or visual impairments that would compromise assessments; (9) do not meet criteria for a substance dependence disorder with less than 30 days abstinence; (10) do not meet criteria for bipolar disorder or psychotic disorders; (11) do not have active suicidal intent indicating significant clinical risk (which would suggest that a treatment specifically targeting this intent was indicated); (12) do not have a major medical condition likely to significantly impact cognitive functioning such as stroke, multiple sclerosis, Parkinson's, brain tumor, or congestive heart failure; (13) are not currently participating in any type of brain stimulation treatment; and (14) are between the ages of 18 to 75 years old. To maximize the generalizability of the study and ensure that we are testing CCT with a typical PTSD Veteran population, exclusion criteria are minimized (e.g., there are no medication exclusion criteria, and Veterans with comorbid depression or anxiety disorders will be included). Current cognitive functioning deficits are also required for participation, and chart review and NSI screening will be implemented for this study.

Informed Consent & HIPAA Authorization

For all studies, written informed consent will be obtained from all Veteran participants who attend in-person visits and electronic informed consent will be obtained through DocuSign for those Veterans who participate by phone or VVC. The consent process will be conducted by trained research team members. Eligible participants will be Veterans with a current diagnosis of PTSD who have been referred for PTSD mental health treatment in the VA Portland mental

health clinics. With approval of the clinical providers, additional eligibility screening will take place for up to 120 Veterans; the Veterans who meet eligibility criteria will be contacted until the desired sample size of 36-48 participants are enrolled in the study. There is currently a waiver of informed consent to be able to review Veterans' medical records to ensure medical inclusion and exclusion criteria are met prior to contacting potentially eligible Veterans. This may reduce time and travel burden for Veterans who do not meet these minimum study criteria. Dr. O'Neil or another study member will let VA mental health clinicians know about the study and inclusion/exclusion criteria and request their assistance in recruiting eligible Veterans. This information will be provided to clinicians in the form of an email, in person conversation, team meeting presentation, or phone call using the attached email letter/script. Veterans meeting these study criteria will be informed of the study by their clinician from the mental health clinic in which they receive mental health treatment. If they are willing to participate, the clinician will notify Dr. O'Neil through CPRS, encrypted email, or in person meeting, or phone call that the Veteran agreed to be contacted about the study. Veterans who express interest in participating will be called to schedule a meeting to discuss and obtain informed consent and to conduct the 90-minute baseline assessment and be randomized to CCT or TAU group if they consent to study participation. During the initial scheduling call, Veterans will be given the option to conduct the baseline visit (i.e., discuss and obtain informed consent and conduct the 90-minute baseline assessment) in person, via VVC, or via telephone; staff will follow current VA guidance about in-person visits and will allow for participant preference when permitted by the VA (e.g., if the Portland VA does not recommend in-person for non-essential visits, then this option will not be offered, and only VVC or telephone appointments will be offered).

If the Veteran chooses to conduct the meeting via telephone or VVC, the study team will schedule a telephone or VVC appointment to go over study documents (i.e., Informed Consent Form and HIPAA Authorization) using DocuSign. An approved study team member will send a DocuSign envelope (an email containing links to the study documents) to the potential participant. The email will contain a reminder for the Veteran to not sign the documents prior to the scheduled contact time, when study staff will review the documents with the Veteran and answer any questions. At the scheduled appointment, approved study staff will contact the potential participant via phone or VVC and use the e-consenting script to walk the Veteran through the DocuSign process, including opening and reviewing the documents. For reference, staff will have opened a copy of the documents on his/her own computer. If the Veteran agrees to be in the study, staff will direct the Veteran to fill in any required fields and sign the document. Once the Veteran has signed the documents, the Veteran will click "Finish" to finalize the documents. While still in the appointment with the Veteran, study staff will verify that the signed documents have been completed accurately and completely as well as signed. Study staff will sign the documents and then direct the Veteran on how to save a copy for his/her own records. After the appointment, study staff will print a copy of the signed documents to be delivered for review to the privacy officer, following the same procedure as in-person visits. The study staff will document the consenting process in CPRS.

If the Veteran chooses to conduct study activities in person and this modality is allowed by the Portland VA at the time, the Veteran will be scheduled for an in-person meeting to discuss and obtain informed consent and to conduct the 90-minute baseline assessment. At all stages of eligibility determination and study involvement, all Veteran participants will be provided an opportunity to have their questions answered.

Risks and Side Effects:

The proposed study poses no serious risks to participants. The study involves direct contact with participants, and there is a slight risk that participants could become upset during groups or assessments or while completing questionnaires. There is also a slight risk that a Veteran could report suicidal thoughts during these contacts, although clinician-patient discussions about mental health or possible suicidal ideation have not been shown to increase the risk of suicide attempts. Participants will be participating in an intervention that has been shown to be acceptable to similar Veteran patients (e.g., those with TBI history), and effective for reducing cognitive problems; however, it is possible that the intervention will not be effective with this population or will produce iatrogenic effects. The risk to participants is minimal but may include breach of confidentiality via inadvertent disclosure of PHI and identifiers and distress upon participating in the CCT intervention.

Protection Against Risk & Participant Safeguards:

Prior to consenting procedures, a waiver for HIPAA will be used to collect Veteran names and email addresses for those who choose to complete study procedures remotely or, in the case of hospital guidance, are unable to complete in-person visits. E-mail addresses will be obtained through the veteran's medical record and verified with the potential participant during the initial phone call. Study staff will not keep a record of Veteran's e-mail address. With the exception of Veteran's name and e-mail address for utilization of DocuSign, no personally identifying information will be released outside of the VA, and all study participants will be assigned unique study ID numbers. Keys linking participant identifiers with study ID numbers will be kept in locked file cabinets in VA research offices or on a password-secure network server, separate from study data. Identifying information will be removed from datasets prior to analyses. All investigators and team members who will have access to the data will have received appropriate VA background checks as part of VA hiring and/or credentialing and will have completed Data Security Training within the prior 12 months. All data will be maintained and analyzed within the secure VA computing system. For all study activities that involve direct contact with participants, all precautions will be taken to ensure confidentiality. For study activities that involve contact with participants via VVC or via telephone, study team members will only contact Veterans from a private area so no one outside of the study team can overhear the conversation or have access to research information or protected health information. The study team member that conducts a study activity via VVC or via telephone will obtain the address of the Veteran's location where they will participate and the contact information of a person at or near the Veteran's location who can be called in the case of emergency. If there is not a person at or near the Veteran's location available in case of emergency, the study team member will notify the Veteran that they will call 911 if there is an emergency and provide the 911 dispatch with the Veteran's address. Veterans will participate via VVC or via phone only if they have a safe, private location from which to participate. No phone, video, or audio contact will be recorded in any way. No research information or protected health information will be written down when conducting the intervention or assessments via VVC or via telephone. These are standard telehealth appointment procedures routinely implemented by Dr O'Neil and other study staff (e.g., Dr. Jason Chen) as part of their clinical service on the rural tele-mental health team at the Portland VA.

Data from Veteran surveys and assessments will similarly be stored in the network file and coded with unique study IDs. Only study personnel will have access to assessment data. Any hardcopies of study survey and assessment data will be kept in locked files in the principal

investigator's office. Special precautions will be taken to minimize Veterans becoming upset and to maximize safety.

During the informed consent process and during ongoing study interactions, members of the study team will ensure that Veterans understand they do not have to answer any question or discuss any topic that they do not wish to answer or discuss. Participants will be provided with emergency contact numbers. All participants will be clearly informed of their right to withdraw from the study at any point without adversely impacting their routine medical, psychiatric, or psychotherapeutic care.

Dr. O'Neil has developed individualized safety plans for use in case patients report active suicidal ideation during interviews. If a Veteran reports current suicidal ideation during an assessment session, interview, or other interactions with members of the study team, study personnel will seek immediate consultation per the safety plan, and work with the patient's referring mental health clinician to ensure that appropriate follow-up assessment is conducted. If a Veteran does not have a current suicide safety plan, the local suicide protocol will be activated if necessary, which involves calling the VA National Suicide Hotline. Hotline staff will be given the caller's name, telephone number, and last four digits of the Social Security Number or as much information that is known at the time of warm transfer. If the VA National Suicide Hotline warm transfer telephone number is busy, study personnel will call 1-800-273-TALK (8255) and press 1 to be routed to the VA National Suicide Hotline. If appropriate and necessary, Veterans with acute suicidal ideation or intent will be escorted to the local VA emergency room and evaluated there by licensed clinicians who will take over their care. Dr. O'Neil has trained many research personnel in procedures for addressing and responding to potential suicidal ideation; all involved study personnel will receive supplemental training in these procedures. For all studies, the study coordinator and the Portland Center's IRB specialist will conduct a review of study files every 6 months to assure compliance with approved procedures, and the local VA research and Development Office will conduct a similar audit annually. In accordance with VA guidelines, a data safety monitoring board will be established.

Adults without decisional capacity will be excluded from this study.

Suicidality*:*

If participants present with high risk for suicide (e.g., report suicidal plans or intentions), study staff will follow the following protocol, one step at a time until the participant is transferred to an appropriate provider for follow-up assessment and care: 1) Contact Dr. O'Neil (PI) or other IRB-approved responsible clinician of the study (e.g., Dr. Jason Chen) to assess the participant and determine if follow-up care is needed (i.e., transfer the participant to the responsible clinician before ending the study visit). 2) Work with the participant to identify and contact their primary VA mental health care provider or medical provider so that s/he can conduct an assessment and provide follow-up care as needed (i.e., transfer the participant to that provider in person before ending the study visit). 3) Walk the participant to the VA emergency room and have emergency personnel conduct an assessment and provide follow-up care as appropriate. 4) If suicide risk becomes apparent while on the phone with a participant and the above steps are not possible, then study staff will follow procedures for a "warm transfer" to VA National Suicide Prevention Hotline staff, using a nationally disseminated protocol described here: *http://www.portland.va.gov/research/documents/hrpp/warm-transfer.doc*. (VA Central Office has arranged with the VA National Suicide Prevention Hotline ((585) 393-7938 OR 1-800-273-8255,

then press “1”) to provide suicide prevention support in cases that a researcher is on the phone with a participant who indicates that they are suicidal. When this occurs, a “warm transfer” should be conducted, which is defined as transferring a call and giving the referring party an opportunity to share information over the phone prior to the call transfer. A warm transfer also allows for all three parties to be on the line at the same time if needed. Instructions for how to conduct a warm transfer if needed during the course of a research study are provided in the above-mentioned website.)

Benefits:

This study will determine whether PTSD-related cognitive symptoms can be treated effectively with CCT, an evidence-based intervention that is effective in other, similar Veteran subgroups, but not yet tested in Veterans who do not have a history of TBI. This study will help determine strategies to facilitate the implementation of CCT in VA mental health clinics. The risk to Veterans, as described above, is low and the proposed study has the potential to considerably improve Veteran care experiences and health outcomes.

Protected Health Information:

As part of the study, we will collect the following individually identifiable health information from each participant: information from their VA Health Records such as diagnoses, progress notes, medication, lab and radiology findings; demographic information such as name, race, gender, age, birthdate, address, phone number, email address, and clinic and research visit dates; social security number and medical record number; questionnaires and neuropsychological measures. This information is necessary for our research, because we plan to use medical record information to identify potential participants and to confirm eligibility for participation in the study. We will use contact information to reach participants and for scheduling. We will use names and email addresses to obtain consent through DocuSign but will not keep a record of email addresses. We will use demographic information to describe our sample (i.e., sample characteristics) and to determine if they moderate study outcomes.

Multi-Site Study Concerns

This is not a multi-site study.

Resources Available

The principal investigator (PI) Dr. Maya O’Neil is a full time, permanent VA clinician, with .5 FTE protected research time (.75 protected research time after initiation of the CDA in January of 2019). Dr. Maya O’Neil and her research team are housed at the VA RR&D National Center for Rehabilitative Auditory Research (NCRAR) and HSR&D Center of Innovation, the “Center to Improve Veteran Involvement in Care” (CIVIC), at the VA Portland Health Care System (VAPORHCS). Dr. O’Neil and Portland mentors and consultants also all have faculty appointments at Oregon Health & Science University, Oregon’s only academic health center, which is physically connected to VAPORHCS. The CIVIC has several PhD-level biostatisticians who support the research of investigators, including Dr. O’Neil; all will be available to her for training and consultation throughout the course of the CDA award. Similar resources will also be available to Dr. O’Neil through the NCRAR. In addition, the VAPORHCS Research & Development Office has dedicated staff to further assist with grant preparation and submission and coordination of travel for research activities.

The PI and her study staff will use the PI's existing personal office (Building 6, Rm 217) and research space as well as Building 104 Neuropsychology Clinic rooms to conduct this research.

Costs To Subjects:

Cost to subjects include their time during study visits, and any costs related to transportation to and from the research visits.

Subject Compensation:

Veteran participants will be compensated with $50 for time and transportation costs associated with completing each of the three 90-minute assessments. Participants' assessment results will also be reported in their VA medical records so that this clinical information can be accessed by them and by their clinicians in the future if needed. There are generally no other direct benefits to participants. However, knowledge obtained from the study may benefit other Veterans in the future. Payment amounts and terms of payment are also listed in the informed consent form.

Participants will be paid the appropriate compensation after the completion of each assessment visit in the study, either by direct deposit (EFT), debit card, gift card, or cash.

Privacy and Confidentiality:

We will take multiple steps to protect participants' privacy and confidentiality. All data will be de-identified, labeled with a code number that is unique to each patient in the study, and maintained in a Subject Data File. All hard copy subject data will be stored in locked filing cabinets in locked rooms, while all electronic data will be stored in password-protected files in a limited access folder on the secure VA network drive. Only IRB-approved study personnel will have access to the Master List key code, Subject Data Files or Informed Consent Forms. We will analyze and report subject data in aggregate form and no PHI will be entered into these analyses or reports. Audio recordings of treatment sessions will be stored on a VA secure server and will be accessed by Dr. O'Neil or her staff for the purposes of rating the group leader's adherence to the treatment manuals.

The PI or project manager will conduct a review of study files every six months to assure compliance with approved procedures. The research team will work closely with the VAPORHCS Information Security Officer to ensure that any data transfer, storage, and handling by non-VA entities adhere to VA security policies.

Participant Routing

As participants are seen within clinical spaces for research visits, and to ensure that participants are in the right area for study visits, participants will check-in with front desk staff/MSAs of the appropriate clinic. Study staff will send appropriate MSAs an encrypted e-mail with participant name, date, and time of study visit to allow MSAs to perform normal clinical duties and assist participants in being routed to study staff.

Information and/or Specimen Management

Study staff is trained on the protocols to ensure that procedures are being conducted within the scope of the approved protocols. Recruitment and enrollment for clinical projects are reviewed regularly at Dr. O'Neil's meetings. At the meetings, staff provide enrollment updates, and the research team problem solves recruitment issues to ensure that projected enrollment numbers

are obtained. The PI or project manager checks procedures (at least monthly) to verify that they are being conducted per the approved protocol, including the responsibilities and roles for gathering and monitoring data. Assessment data are recorded by research staff as it is collected, and data accuracy is verified by double scoring, data entry and visual verification.

All recruitment data containing PHI will be stored on VINCI servers at the Austin Information Technology Center, 1615 Woodward St., Austin, TX 78772-0001. The specific server where the data will be stored will be chosen by VINCI personnel. The server name and location within the Austin Information Technology center may be changed at any time at the discretion of VINCI personnel.

In addition, all recruitment data containing PHI downloaded from the VINCI server will be stored in a password protected file on the PI's secure research folder and only approved study personnel will have access to this folder. This data will be used for recruitment purposes only. Research staff will use an audited VINCI download utility to move these data from VINCI servers to local storage media on the VA servers behind the VA firewall. Only study team personnel explicitly authorized by data stewards will have access to the recruitment data. The study principal investigator has the responsibility for security of the study. VINCI data managers and VA OI&T personnel not under the purview of the study principal investigator control the servers, network, processors, firewall, and software in the VINCI environment, including access rights granted to study personnel.

Data Management: We will use Microsoft Excel to record and store study data, track subject screening, enrollment and participation, create surveys, generate reports, and enhance project management. Project computers are served by the VAPORHCS local area network and all database and qualitative analysis software are licensed. All information linking study data to personal health information will be stored on a password-secure server behind the VA firewall, or in hardcopy form in locked file cabinets which reside in a locked office in a secure research building (Building 6). All records will be maintained according to the VHA records control schedule. Audio recordings will be made to ensure that the study team member who is running the CCT group is adhering to the CCT manual (fidelity monitoring). Once audio recordings have been reviewed by study staff for the purpose of fidelity monitoring, the recordings will be stored according to the VAPORHCS records control schedule.

We are also asking participants to allow their data and contact information including identifiers to be stored ('banked") in the Neuropsychology Data Repository (MIRB# 3508) located at the VA Portland Health Care System (VAPORHCS) and managed by Dr. Maya O'Neil. These data will include data resulting from the cognitive test battery and identifiers including name, telephone number, the last four digits of social security number, and study participation dates that will be used in future research. Contribution to the repository is optional.

Transfer of Data Ownership

N/A

Data and Safety Monitoring Plan (DSMP)

Safety Monitoring: The PI or anyone else who has contact with study participants during study activities have the responsibility to monitor for any potential adverse events and protocol

deviations. Any adverse participant event will be reported immediately to PI Dr. O'Neil, who will contact the participant and determine if additional intervention is needed to ensure participant safety. Protocol deviations will also be immediately reported to Dr. O'Neil who will ensure that adverse events deemed to be unanticipated problems and protocol deviations are properly reported to the IRB in a timely manner. Detailed written documentation will be kept for all adverse events that occur over the course of the study. PI Dr. O'Neil holds weekly meetings with lab personnel where they will discuss adverse events and protocol deviations associated with this project and ways to reduce repeat occurrences. Research staff will examine all cumulative adverse events quarterly to determine if there are any systematic problems and to implement protocol corrections as needed after receiving IRB approval.

Data Monitoring: All information linking study data to PHI will be kept within VHA electronically in secure computer files stored behind firewalls requiring password access, or in hardcopy form in locked file cabinets in locked offices. All patient identifiers will be removed prior to analysis. All investigators and team members who will have access to the data will have received appropriate background checks as part of hiring and/or credentialing and will have completed Data Security Training within the prior 12 months. The PI or project manager will conduct a review of study files every six months to assure compliance with approved procedures. The research team will work closely with the VAPORHCS Information Security Officer to ensure that any data transfer, storage, and handling by non-VA entities adhere to VA security policies.

Per VHA guidelines, data resulting from this study will be stored locally on VHA password-secure folders until enterprise-level resources become available for long-term storage and access. Requests for data access will be considered and responded to within one month of the request and datasets will be made available electronically. Requests must be made in writing to the study PI and provide information on the purpose for accessing the data.

All data used in final, published results will be made available for sharing. Published data will be available upon request to any investigator in order to enable independent validation and interpretation of published data.

Once the current study is closed, we will store de-identified, anonymized dataset in an approved data repository consistent with policies in 1200.12 (Use of Data and Data Repositories in Research). A sharing agreement will prohibit the recipient from identifying or re-identifying (or taking steps to identify or re-identifying (or taking steps to identify or re-identify) any individual whose data are included in the dataset.

Step-by-Step Guidance on Conducting the Study

See section above on study methods which includes step by step guidance on study conduct and procedures.

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Appendix – Supporting Documents List

- CCT Manual
- Phone/In Person Recruitment Script
- Email Message for Recruitment
- Participant Recruitment flyer