D3395-W, Optimizing Cognitive Remediation in VA Mental Health Rehabilitation Settings
NCT04395157

Study Protocol and Statistical Analysis Plan

10/30/2025

Over one hundred thousand Veterans annually utilize mental health residential rehabilitation programs (RRTPs) and psychosocial rehabilitation and recovery centers (PRRCs). Through support and comprehensive programming, these mental health rehabilitation milieus help Veterans with mental illness overcome barriers to community reintegration. Despite the success of these milieus, cognitive impairment is commonly observed in Veterans with mental illness, reduces gains from programming, and limits successful recovery. Cognitive impairment is a common transdiagnostic illness dimension conferred both directly and indirectly by mental illnesses. Cognitive rehabilitation through remediation strategies can potentially attenuate cognitive impairment for these Veterans and improve outcomes, but there are two inter-related problems that limit the effectiveness of such interventions. First, we are not able to identify which Veterans will benefit from mental health rehabilitation programming at program entry. Second, we are not able to predict which Veterans are going to benefit from any specific cognitive remediation intervention.

This CDA-2 application seeks to test whether an electroencephalographic (EEG) biomarker, mismatch negativity (MMN), can be used to predict Veteran recovery in mental health rehabilitation treatment settings, and identify Veterans who will respond to cognitive remediation interventions. MMN is an event-related potential which is considered to be a biomarker of information processing, linked to cognition in healthy subjects and cognitive impairment in a variety of neuropsychiatric illnesses. MMN also mediates psychosocial and functional outcomes in individuals without any psychiatric comorbidities and individuals with mental illness. Recent work also suggests that MMN can identify individuals who will experience gains from a full course of cognitive remediation when measured over the first hour of cognitive remediation. These biomarker relationships (cognition, cognitive remediation sensitivity, functioning) have not yet been definitively established in a heterogenous Veteran population receiving care in real-world settings like RRTPs and PRRCs.

Veterans with mental illness will be recruited from the VA San Diego Healthcare system RRTP and PRRC at program entry. Baseline measures of functioning, psychosocial disability, cognition and treatment engagement will be collected. Following these assessments, Veterans will undergo testing to collect MMN data, and then will be challenged with a one-hour cognitive remediation exercise, which is a typical component of full multi-hour cognitive remediation programs. Veterans will be followed with monthly assessments of psychosocial disability and treatment engagement. At the end of study, functioning will also be re-assessed.

If successful, results from the studies proposed will create an objective, precision-medicine platform which could fundamentally change how RRTP and PRRC approach rehabilitative programming for Veterans with mental illness. In carrying out the studies proposed, the PI will gain critical training in advanced EEG biomarker analyses, computational/statistical methodology and clinical trial design and implementation which will expand his scientific skill set and lead to scientific independence. This CDA-2 will allow the PI to work towards his career goal of using EEG biomarkers to personalize cognitive rehabilitation interventions for Veterans with mental illness.

Veterans with mental illness face challenges with community reintegration, including achieving vocational success, attaining their educational goals and going back to school, and maintaining a high quality of life. VA mental health Residential Rehabilitation Treatment Programs and Psychosocial Rehabilitation and Recovery Centers are designed to help Veterans overcome these barriers, but cognitive impairment often seen in Veterans with mental illness limits gains from these settings. Cognitive remediation interventions can be helpful, but they are either “one-size fits all,” and thus may not be useful for all Veterans with mental illness, or are too narrow in scope, focusing on specific mental illnesses, limiting generalizability. This project will test whether an objective biomarker can better match the “right” Veteran to the “right” cognitive remediation treatment regardless of their specific mental health diagnosis. Information gained from this study will help establish a precision-medicine approach towards cognitive rehabilitation for Veterans with mental illness.

SPECIFIC AIMS

Hundreds of thousands of Veterans annually utilize mental health residential rehabilitation treatment programs (RRTP) and psychosocial rehabilitation and recovery centers (PRRCs) across >200 medical centers. RRTPs and PRRCs help functionally disabled Veterans with mental illness acquire new skills, make use of vocational services, and manage symptoms. Despite the menu of rehabilitation programming offered in these settings, the cognitive impairment commonly observed in this population, reported in up to 80% of Veterans in these settings, limits engagement in recovery-oriented activities, reduces gains from rehabilitative activities and jeopardizes functional outcomes. **Developing interventions to address cognitive impairment in order to improve outcomes would be beneficial to Veterans who make use of RRTP and PRRC services.** However, at present there are key challenges limiting such needed innovation**:** first, there are no objective measures to help identify at program entry which Veterans will have a positive recovery trajectory; second, there are no objective measures to predict which Veterans will favorably respond to interventions aimed at improving cognitive functioning.

To address these issues, our group has studied an EEG biomarker - **mismatch negativity (MMN)** - to better select the "right" individual for the "right" pro-cognitive intervention to improve outcomes in real-world treatment settings. Pre-treatment measures of MMN predict 1) performance on cognitive remediation exercises during the first training session, and 2) cognitive benefit after 30 hours of training (3 months later) for individuals with mental illness in community treatment settings. **Gains from these cognitive remediation training programs in community-based mental health residential settings are associated with increased milieu therapeutic, social, and vocational activities, and linked with improved quality of life.**

MMN demonstrates high test-retest reliability, is validated for multi-site studies, and can be collected by non-specialists. MMN mediates psychosocial outcomes, including measures of overall functioning in patients with mental illness. MMN is also associated with cognitive functioning not only in healthy subjects, but also in those suffering from specific neuropsychiatric illnesses. These lines of evidence suggest that MMN can be used to objectively identify which individuals with mental illness will benefit from community-based mental health services and resources, and can distinguish who may benefit from pro-cognitive interventions. **However, before biomarker-guided precision medicine approaches are ready to be deployed in VA settings, two key questions must be answered**: 1) Is MMN associated with functioning and recovery trajectory in VA mental health rehabilitation programs? and, 2) Can MMN predict sensitivity to cognitive remediation in a heterogenous group of Veterans with mental illness?

In order to answer these questions we will recruit Veterans with mental illness engaged in VASDHS RRTP/PRRCs (n = 104) within the first month of entry into these programs. MMN, cognition, psychosocial disability, treatment engagement and functional performance will be assessed. Veterans will also undergo one hour of cognitive remediation exercises which are typical components of therapeutic 30-hour courses of cognitive remediation. Veterans will be followed monthly for a total of 4 months.

Data obtained from this CDA-2 will form the core of a precision-medicine approach for Veterans with mental illness engaged in rehabilitation programming in RRTPs and PRRCs across the VA Healthcare System, while simultaneously providing a rich training opportunity to launch my career as a VA clinical scientist. The Specific Aims of this proposal are:

Specific Aim 1: Determine whether MMN is related to functioning, psychosocial recovery and treatment engagement in VA rehabilitation milieus. We hypothesize that greater MMN amplitude will predict improvement on functional performance, reduced psychosocial disability and greater treatment engagement over 4 months.

Specific Aim 2: Determine whether MMN is linked to cognition and predicts cognitive remediation exercise performance in a heterogenous group of Veterans with mental illness. We hypothesize that MMN will correlate with global cognition and that higher performance on a one hour cognitive remediation exercise will be predicted by greater MMN amplitude. Recent work has identified demographic factors that affect performance on cognitive remediation, including age, cognition, and anticholinergic medication burden. We hypothesize that these factors affect cognitive remediation performance in this Veteran population.

Exploratory Aim: Assess feasibility and acceptability of using biomarker-guided cognitive rehabilitation interventions in VA rehabilitation settings. We will assess Veteran motivation and interest in undergoing EEG biomarker assessment prior to a cognitive remediation program. We will also interview staff and clinicians at each site to identify ways to optimally deploy future biomarker-informed cognitive remediation trials.

2.1 BACKGROUND AND SIGNIFICANCE

2.1.1 SIGNIFICANCE

VA mental health rehabilitation settings are necessary to help Veterans with mental illness overcome psychosocial disability. More than one out of three Veterans are thought to need mental health services and more than one out of every four U.S. Veterans is diagnosed with a mental illness, including: anxiety and post-traumatic stress disorders (PTSD), mood disorders (e.g., major depressive disorder, MDD; bipolar affective disorder, BAD), and chronic psychotic disorders (e.g., schizophrenia, SZ and related disorders). [1, 2] Veterans with mental illness account for >30% of those with a service connected disability rating between 50-90, and >50% of those with a rating of 100 [3, 4]. Veterans with mental illness also account for up to 80% of unemployed Veterans, >50% of Veterans who are disabled or unable to work and are at high risk to be homeless[4-6]. In order to address these challenges, the Veterans Health Administration (VHA) has established mental health Residential Rehabilitation Treatment Programs (RRTPs) and Psychosocial Rehabilitation and Recovery Centers (PRRCs) to help Veterans with mental illness acquire skills and receive support to improve successful community reintegration. In total, hundreds of thousands of Veterans with mental illness utilize RRTPs and PRRCs annually, which currently operate at >200 sites associated with VA medical centers.

Cognitive impairment is a core transdiagnostic illness dimension in Veterans with mental illness and severely limits community reintegration. Although the pathophysiology of mental illnesses commonly observed in Veterans are distinct, myriad and complex, cognitive impairments have been widely reported in each condition. Even though the specific constellation of cognitive impairment differ by illness (see Table 1), they converge to result in moderate-to-severe impairments in global cognition[7, 8]. These deficits are magnified with co-morbidities found at relatively high rates in Veterans with mental illness: medical/neurological illness including traumatic brain injury (TBI), physical disabilities, substance use, and stressors including homelessness [9-14]. Clinically significant cognitive impairment has been reported in up to 80% of Veterans with mental illness who use mental health rehabilitation services [15].

	Attention/Vigilance	Working Memory	Executive Functioning	Episodic Memory	Semantic Memory	Visual Memory	Verbal Memory	Fear Extinction	Processing Speed	Procedural Memory	Social Cognition	Language
PTSD	+++	+	+	++	+	+	++	+++	+	0/+	+	+
Psychosis	+++	+++	+++	+++	++	+	+++	++	++	+	+++	+++
Anxiety	++	+	0/+	0/+	0/+	0/+	+	+	0/+	0/+	0/+	0/+
BAD	++	++	++	++	+	+	++	+	++	0/+	++	++
MDD	+	++	++	++	+	+	+	0/+	++	+	+	+

Table 1. Overview of cognitive impairment in PTSD, chronic psychotic disorders (e.g., SZ), anxiety disorders (including generalized anxiety disorder and panic disorder), and mood disorders (BAD, MDD). Adapted from Millan et al. 2012[6]

+++ = core, severe, virtually universal deficit + = present, but may not be pronounced
++ = common, marked characteristic 0/+ = mild, poorly documented or absent.

Yet, regardless of whether cognitive impairment is central to the disease processes underlying mental illness (for example, with chronic psychotic disorders), or driven by symptoms of mental illness (as with cognitive impairment in MDD), it predicts poor outcomes. Cognitive impairment is associated with compromised ability to achieve independent living, limited vocational success, and reduced quality of life[16-18]. Furthermore, cognitive impairment limits engagement in medical and mental health treatment as well as reduces successful utilization of rehabilitative programming such as those found in RRTPs and PRRCs[19, 20].

Addressing cognitive impairment can improve community reintegration but it is not clear which cognitive remediation strategies are ideal for use in VA mental health rehabilitation settings. Cognitive remediation strategies have demonstrated efficacy in reducing cognitive impairment in patients with mental illness, and individuals with the most severe cognitive impairment tend to experience the greatest gains[20-28]. Strategies range from compensatory cognitive training, where skills and habits are taught in an effort to

overcome functional deficits resulting from cognitive impairment; “drill-and-train” programs, which focus on improving specific cognitive domains; and “bottom-up” cognitive training approaches, where basic sensory processes are enhanced to yield improvements in higher-order cognitive function. In ideal settings, these cognitive remediation strategies improve functional outcomes, including enhancing quality of life and reducing disability for those with mental illness [25, 28-30]. However, these studies typically have significant rates of treatment non-response, have limited success when translated from academic labs to real-world mental health treatment settings, or fail to replicate when expanding from small single-site trials to larger multi-site trials[29, 31, 32]. Evaluating the usefulness of various cognitive remediation strategies is also made difficult due to the sheer volume of interventions, which have expanded considerably in the last decade [33]. These strategies now span the gamut from smart phone apps, to websites, handheld and console-based games, and laptop/computer-based platforms[34, 35]. Thus, while cognitive remediation strategies have the potential to be helpful to Veterans with mental illness, it is difficult to evaluate 1) which Veterans will respond to specific cognitive remediation interventions, 2) whether a positive response to a cognitive remediation intervention augments gains from VA mental health rehabilitation programming, and 3) whether gains from VA mental health rehabilitation programming imparted by cognitive training enhances psychosocial success for Veterans.

The central problem: there are currently no objective measures which can help determine which cognitive remediation interventions should be used in VA mental health rehabilitation settings in order to improve community reintegration for Veterans with mental illness. Objective measures would help better match the “right” cognitive remediation intervention to the “right” Veteran and inform a precision-medicine approach to rehabilitation in RRTPs and PRRCs. Ideally, objective measures would 1) identify which Veterans with mental illness are at risk for poor gains from rehabilitation at program entry, and, once these Veterans are identified, 2) predict which of these Veterans would benefit from a cognitive remediation intervention to improve gains from rehabilitative programming. If such objective measures are identified, they can be used to better evaluate cognitive remediation strategies for use in VA mental health rehabilitation settings.

2.1.2 INNOVATION

The core innovation of this application is that it will establish whether an EEG biomarker – mismatch negativity (MMN) – can identify Veterans with mental illness at risk for limited gains from rehabilitation programming, and predict which Veterans will respond to cognitive remediation.

This innovation will advance the field of cognitive rehabilitation by creating a platform on which current cognitive remediation strategies can be evaluated and future novel pro-cognitive strategies can be developed. The studies proposed will help establish a precision-medicine approach to cognitive rehabilitation whereby Veterans will receive personalized cognitive interventions as opposed to inefficient “one-size-fits-all” approaches. Possessing an objective biomarker that can identify Veterans with mental illness at risk for limited gains from rehabilitation programming will also improve treatment response in future cognitive remediation trials, improve translation of results from efficacy trials conducted in laboratory environments to effectiveness trials carried out in usual treatment settings, helping scale-up promising interventions.

2.1.3 RELEVANCE TO VETERAN HEALTH, IMPACT ON VA REHABILITATION PROGRAMMING, AND IMPORTANCE TO VA HEALTHCARE SYSTEM

This application directly addresses the VA RR&D priority area of enhancing community reintegration through cognitive/psychological rehabilitation. If successful, this application will allow the VA research community to better evaluate cognitive remediation interventions and their impact on outcomes for Veterans with mental illness by using an objective EEG biomarker. RRTPs and PRRCs will be able to create more impactful rehabilitative programming by more effectively implementing high-yield interventions, and de-implementing lower-yield interventions. The scientific products from this application will help maximize the returns on resources, staff and funds the VHA has invested into RRTPs and PRRCs, and capitalize on Veteran time and energy spent in rehabilitative programming. The knowledge gained from the studies proposed will not only be relevant to the VA San Diego Healthcare System where it will be conducted, but also will be able to translate to RRTPs and PRRCs VA-wide.

2.1.4 BACKGROUND

Mismatch negativity (MMN): an EEG biomarker of cognitive functioning

Mismatch negativity (MMN) is an event-related potential (ERP) evoked on electroencephalography (EEG) when a train of standard stimuli is interrupted by an oddball, or "deviant", stimulus. MMN is pre-attentive, reflecting an automatic response to sensory stimuli, and is able to be elicited without any effort, behavioral response, or conscious awareness [36, 37]. MMN can be evoked via multiple sensory modalities, but MMN evoked by auditory paradigms represents the vast majority of MMN literature [38] (see Figure 1). Deviant stimuli only need to differ from stimuli in one dimension (i.e., pitch, volume, timbre, or duration) to elicit a reliable MMN response. MMN is reported as a negative value.

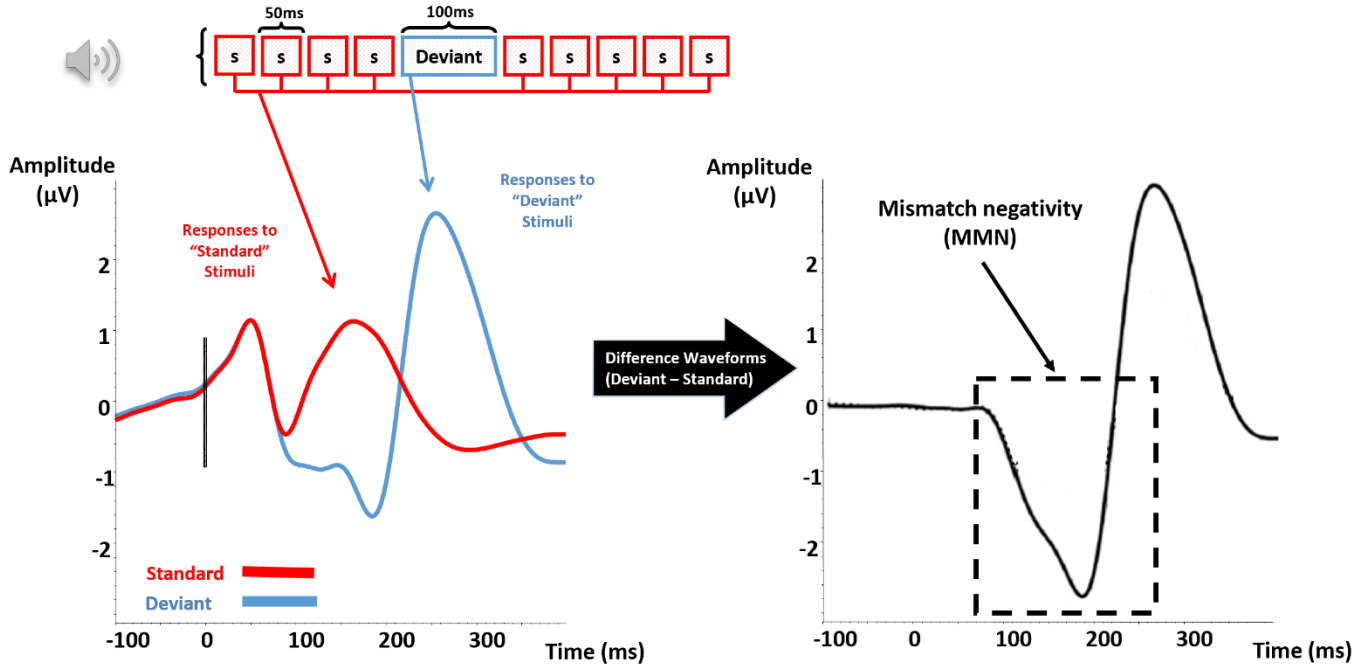


Figure 1. Mismatch negativity. Compared to event-related potentials evoked from "standard" sound stimuli ("s"; in red), rare "deviant" stimuli (blue) evoke event-related potentials that are characteristically different between ~100 to 200 ms after stimulus onset. The difference waveform resulting from subtracting standards from deviants yields mismatch negativity (MMN) in the ~100 to 200 ms time window, a negative amplitude value. In this example, standard stimuli only differ from deviant stimuli in duration (50 vs 100 ms in length).

MMN represents the first objective index of sensory discrimination that occurs when input from the external environment enters the central nervous system. The ability to identify and differentiate small changes in sensory information is a key aspect of all neural systems, and as such, MMN (or analogous electrophysiological correlates) has been described not only in humans, but also in monkeys, rodents, birds and amphibians [39-41]. Since appropriate sensory discrimination underlies all higher order cognitive processes, including attention, memory, emotion/social cognition, and executive functioning, MMN has been described as "primitive sensory intelligence," and is thought to reflect general brain plasticity [42]. In humans, the MMN response is thought to be generated from a number of different brain regions distributed across cortical and subcortical regions (see Figure 2), and involve modality-specific primary and secondary association cortices. Previous work has consistently localized auditory MMN to be distributed across fronto-temporal regions[43].

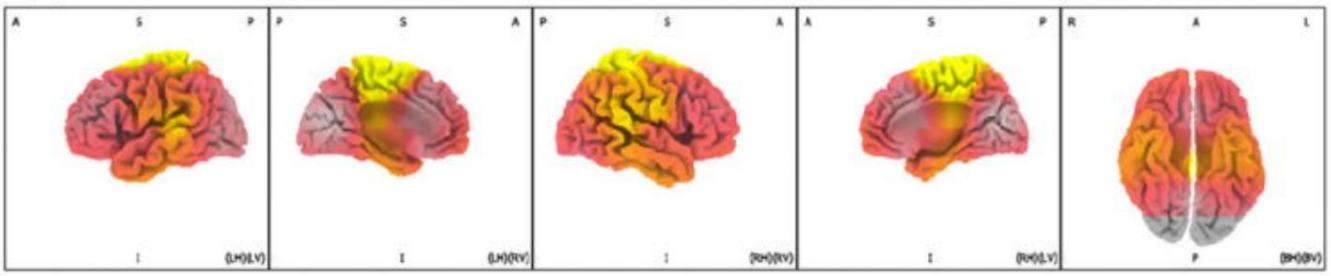


Figure 2. Brain regions involved in the MMN response. Yellow regions indicate areas of high current density associated with MMN including temporal, frontal and parietal regions. Adapted from Takahashi et al. 2013[44]

MMN is abnormal in multiple psychiatric diseases and is linked to psychosocial outcomes.
MMN abnormalities have been repeatedly linked to multiple impairments in processing speed, attention, verbal and working memory, fluency and social cognition[45-48].MMN amplitude abnormalities have been reported in psychotic disorders for nearly three decades in hundreds of publications: they are observed in patients with chronic illness, those who have been medicated with antipsychotics, unmedicated patients, those at high risk for conversion to psychosis, and in first degree relatives of patients with chronic psychotic disorders [49, 50]. Several studies have reported abnormalities in MMN in mood disorders, and to mood-associated neurocognitive deficits. Reduced MMN amplitude has been described in patients in the first episode of depression, as well in those with recurrent MDD; attenuation of MMN amplitudes have been linked to impaired processing of emotional stimuli in patients with MDD, even in patients with MDD who are in remission[51-54]. Patients with BAD have MMN abnormalities compared to healthy non-psychiatric subjects, but are less impaired than patients with psychotic disorders (consistent with genetic studies linking psychotic disorders with bipolar disorder) [54-56]. Limited studies have been carried out investigating MMN in PTSD and anxiety disorders: while varying MMN paradigms have been used in these studies, they seem to generally support the association between abnormal MMN and trauma-associated or anxiogenic- stimuli, with either mild or no deficits to neutral stimuli [57-60]. Both acute and chronic alcohol use is associated with diminished MMN, which is associated with memory impairments and processing speed [61-63]. Hallucinogenic or psychotogenic substances (e.g., ketamine, PCP) also produce MMN abnormalities similar to those with psychotic disorders[64, 65]. Chronic cannabis users have impaired MMN, but not casual users, and MMN returns to normal values with continued abstinence[66-68].

MMN correlates with global assessment of functioning in adults without any psychiatric diagnoses [69]. Additionally, abnormal MMN is associated with social, occupational and overall disability; reduced quality of life; impairments in functioning in patients with psychotic and mood disorders[70-72]. As exemplars, Figures 3 and 4 show such a relationship between MMN and global assessment of functioning in healthy non-psychiatric subjects and patients with schizophrenia[69, 72].

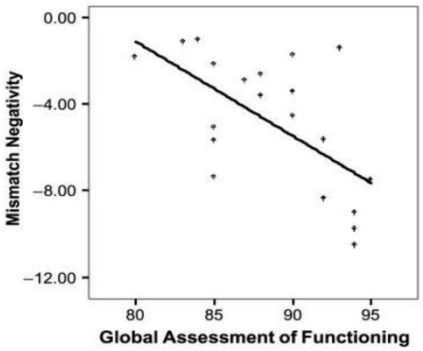


Figure 3.
Relationship between MMN and global assessment of functioning in healthy non-psychiatric subjects

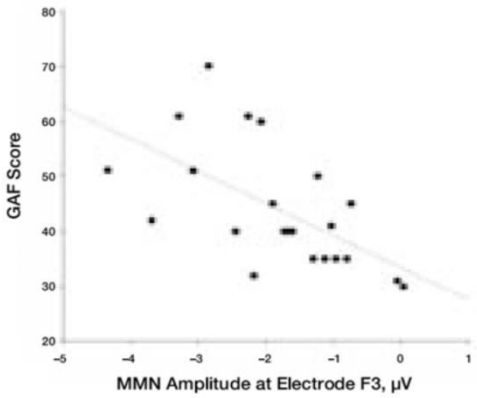


Figure 4.
Relationship between MMN and global assessment of functioning in patients with schizophrenia

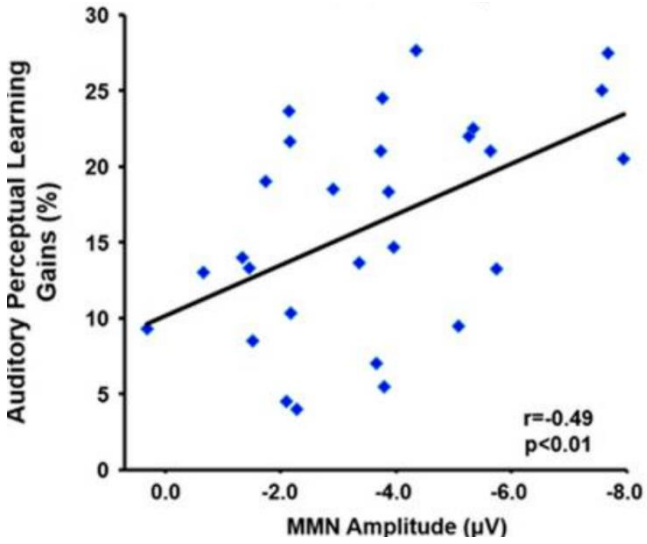
MMN has been tested in large multi-site trials, has high test-retest reliability, is a candidate biomarker for pro-cognitive therapeutics.
MMN has been tested in large multi-site trials in both patients with mental illness as well in subjects without psychiatric history. One of the largest studies to utilize MMN as a routine biomarker has been the Consortium on Schizophrenia Genetics (COGS) study [73]. In this study, 1800 subjects were recruited across 5 sites (UCSD, UCLA, University of Washington, University of Pennsylvania, and Mount Sinai School of Medicine). In this study, where EEG was collected by non-specialists who had received ~2.5 hours of training, site only accounted for ~1% variance in aggregate data. MMN has also demonstrated high test-retest reliability with a one year intraclass correlation coefficient of > 0.8. Based on the ability of MMN to index cognitive functioning, the link between MMN and functional outcomes, and the ability of MMN (or MMN analogues) to be elicited in lower-order model system, MMN is thought to be an ideal biomarker for screening and testing pro-cognitive therapeutics [74, 75].To that end, our group has detailed how memantine, a cognition-enhancing medication commonly used in the treatment of Alzheimer's disease, can improve MMN deficits in patients with schizophrenia[76].

2.2 PRELIMINARY STUDIES

Adding to the literature, we have investigated whether MMN can be useful in predicting response to and gains from a cognitive remediation intervention in patients with schizophrenia. Below we describe the principal findings, which are all published.

MMN predicts performance on a one hour cognitive remediation exercise

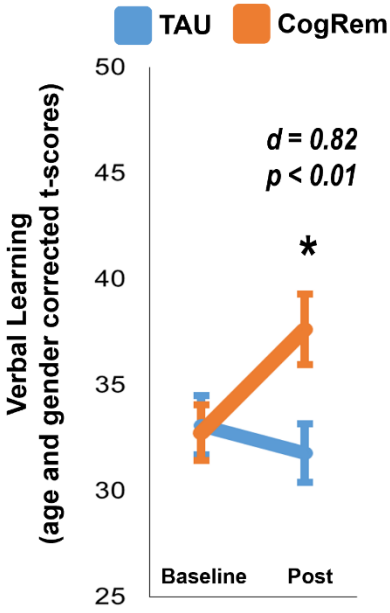
Figure 5



We assessed MMN in patients with schizophrenia (n = 28) prior to completing one hour of cognitive training delivered via the Posit Science/BrainHQ computerized cognitive remediation platform as reported in Perez et al., 2017[77]. In this task, participants listened to a series of two successive tone sweeps (varying in frequency range and interstimulus interval (ISI)), and then indicated with two corresponding button presses whether the frequency increased or decreased within each tone, respectively. The exercise contained multiple stimulus sets composed of combinations of base frequency and duration. Subjects completed stimulus sets with longer-duration stimuli before stimulus sets with shorter-duration stimuli are made available. Auditory exercises were psychophysically adaptive, and task difficulty increased and decreased systematically and parametrically with performance changes. These exercises were comfortably tolerated by all subjects. Auditory perceptual learning gains for each subject were defined as the mean percentage of improvement in auditory perceptual learning speed on psychophysically smaller threshold differences in tone duration and frequency. As seen in Figure 5, we found that larger auditory perceptual gains on a one hour cognitive remediation exercise were associated with larger pre-training MMN amplitudes. These findings suggest that MMN can predict performance on cognitive remediation exercises used in cognitive remediation programs.

MMN predict cognitive gains after a full course of cognitive remediation

Figure 6

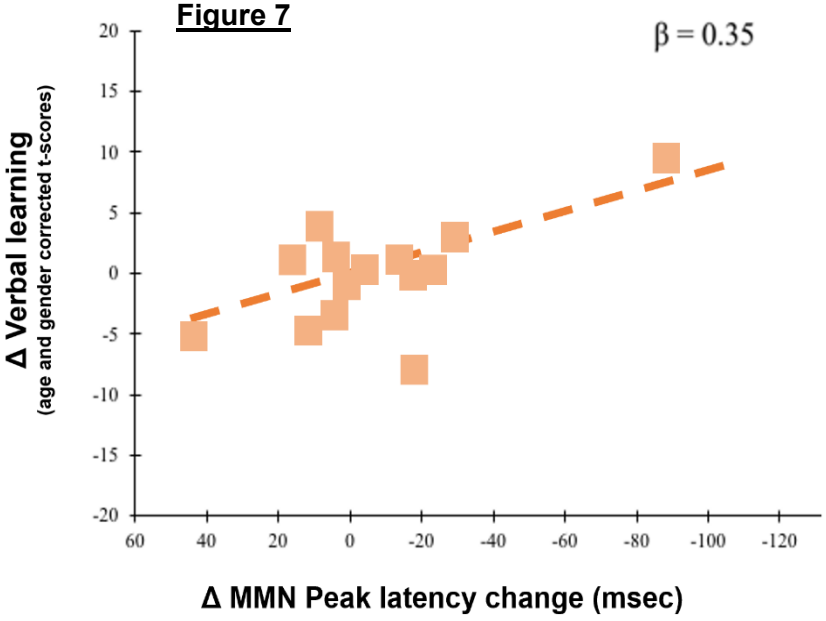


We were encouraged to find that MMN predicts response to a one hour cognitive remediation exercise. We then wanted to investigate whether early changes in MMN predicted gains after a full course of cognitive remediation (using the same cognitive remediation program as above). Since previous studies had reported that cognitive remediation exercises improved cognition in participants in academic labs, we wanted to see if this was also true in usual care mental health rehabilitation settings.
As reported in Thomas et al., 2018[29], we carried out a full 30 hour cognitive remediation training program at a locked inpatient residential treatment facility, recruiting participants with chronic psychosis. These patients were severely ill, and so gravely disabled by their symptoms that they were under permanent conservatorship . Participants were randomized to treatment as usual (TAU, n = 22) or TAU with 30 hours of cognitive remediation (CogRem, n = 24). CogRem participants underwent cognitive training in 1 hour blocks, up to three times a week, and on average required 3 months to complete the full course.

At follow up, as shown in Figure 6, we found that participants in the CogRem group had made significant gains in verbal learning, with a large effect size, compared to TAU.

In a subset of participants in this study who underwent cognitive remediation, we measured MMN changes before and after one hour of cognitive training. We then asked whether these initial MMN changes from the first hour of training predicted benefits after a full 30 hours of training. As reported in Hochberger et al., 2019[31], and represented in Figure 7, we found changes in MMN peak latency measured after the first hour of training significantly correlated with changes in verbal learning, 3 months later (after 30 hours of training, $p<0.05$). Additionally, our recently submitted, unpublished, analyses have also revealed that MMN and related EEG metrics measured over the first hour of training predict clinical improvement from cognitive remediation with a sensitivity of >90% and a specificity of >80% (data not shown).

Figure 7



These findings suggest that MMN measured at study entry can predict gains from a full course of cognitive remediation in usual care mental health rehabilitation settings.

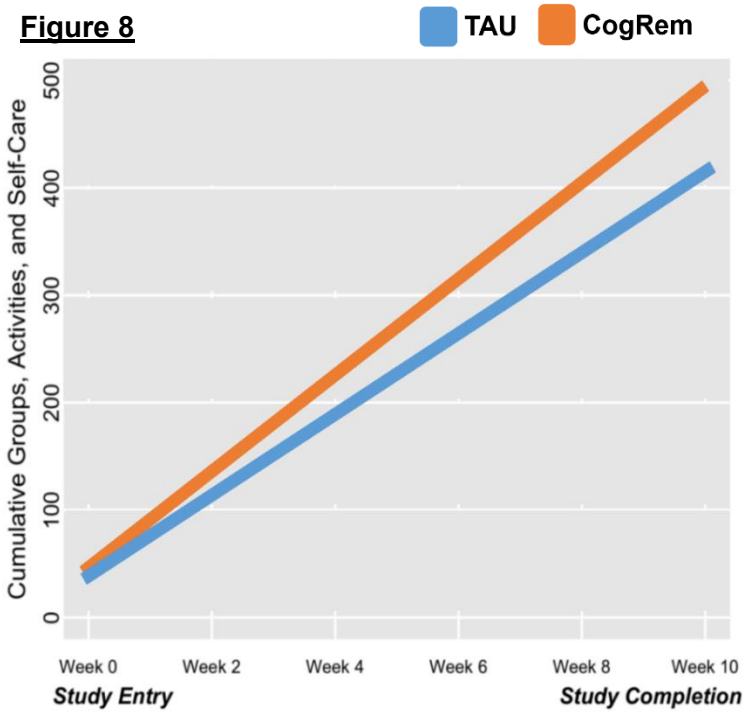
Cognitive remediation is associated with increased treatment engagement

Based on our knowledge of MMN, its relationship to cognitive functioning, and its association with outcomes, we next asked if gains imparted by cognitive remediation generalized to more distal endpoints in the study described above. We were interested in seeing if gains in cognition translated to greater engagement in rehabilitation.

We were able to track cumulative rehabilitative activities in this residential treatment center including: groups attended, therapeutic activities engaged, and self-care activities recorded by staff.

As shown in Figure 8 (adapted from data published in Thomas et al., 2018[30]), the CogRem group cumulatively accrued more rehabilitative activities than the TAU group. Specifically, the 30 hours of cognitive remediation in the CogRem group yielded an average of one extra week of total rehabilitation per participant over the course of the study compared to the TAU group.

Figure 8



These findings suggest that gains from cognitive remediation can generalize and enhance recovery in usual care mental health rehabilitation settings.

In total, taking into account previously published literature, and these preliminary studies, MMN is a robust general biomarker of sensitivity to cognitive remediation.

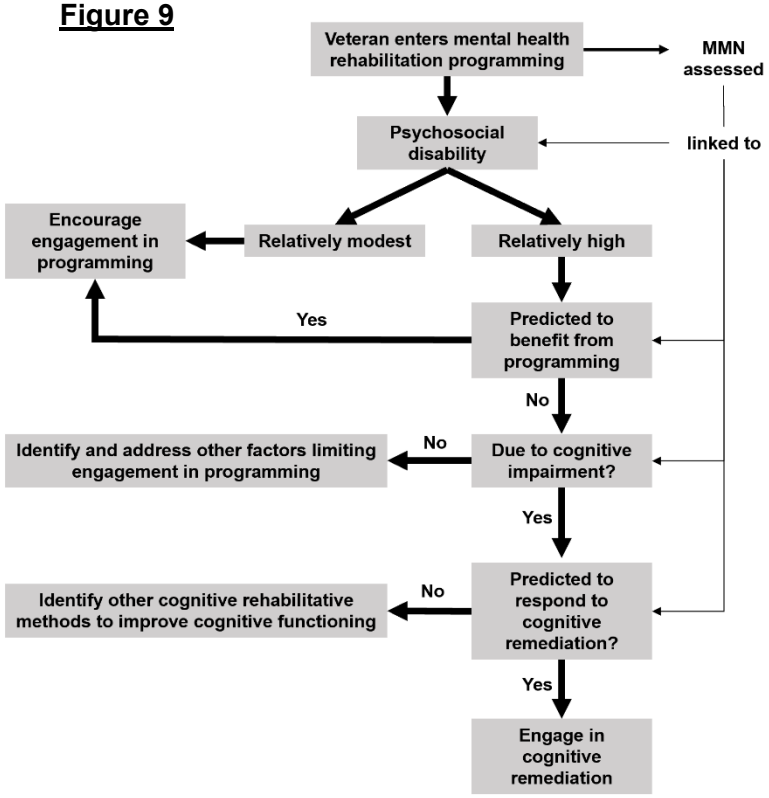
2.3 STUDIES PROPOSED

2.3.1 Rationale for studies proposed

The preliminary studies we have already conducted have supported a link between MMN and cognitive remediation exercise performance, and between cognitive remediation gains and enhanced mental health rehabilitative milieu engagement. Previously published literature has also described the link between MMN and psychosocial disability. Together these studies would suggest that MMN may be useful in better identifying and characterizing Veterans at entry into mental health rehabilitation programming that have high psychosocial disability, who may not be able to maximally benefit from rehabilitative programming due to cognitive impairment, and who may be responsive to cognitive remediation.

Using MMN in mental health rehabilitation milieus in such a way would enhance efforts to maximize gains from programming and better aid these Veterans in successfully achieving community reintegration. An idealized schema depicting a future MMN-guided approach toward rehabilitation is shown in Figure 9.

Figure 9



However, before MMN can be routinely used as part of a precision medicine approach for cognitive remediation in VA mental health rehabilitation settings, two critical questions must be answered:

1) Is MMN associated with overall functioning and recovery trajectory in VA mental health rehabilitation settings?

2) Can MMN predict response to cognitive remediation in a heterogenous group of Veterans with mental illness?

Indeed, Veterans have unique constellations of medical and mental healthcare needs that put them at greater risk for psychosocial disability than their civilian counterparts. Consequently, programming in VA mental health rehabilitation settings (PRRC and RRTPs), is focused on the unique needs of Veterans. How these factors affect the relationship between MMN, psychosocial disability and outcomes has not been characterized in Veterans to the best of our knowledge. Additionally, Veterans have unique co-morbidities (discussed above) which would contribute to cognitive impairment in ways beyond those imparted by mental illnesses in civilian populations. **Thus, without having clear answers to these two questions, a full scale MMN-guided cognitive remediation trial is not yet warranted in VA mental health rehabilitation setting for Veterans with mental illness.**

2.3.2 Synopsis of research proposed and considerations taken into account in designing the study

We will assess MMN, cognition and functioning in Veterans with mental illness recruited at entry into VASDHS's PRRC and RRTP. We will then assess performance on a one hour cognitive remediation exercise. We will follow these Veterans for three additional monthly assessments of psychosocial disability and treatment engagement for a total of 4 months of study. The design of this study and Specific Aims will address knowledge gaps described above.

The main goal of recruiting from two rehabilitation milieus, with different constellations of mental illness diagnoses (see below), is to test and extend the generalizability of MMN as a useful biomarker. This is also central to my training and future career goals of becoming an expert in developing and using biomarker-guided cognitive rehabilitation interventions across VA treatment milieus. Additionally, there are secondary reasons for using two milieus: 1) to increase the range of functioning at baseline in order to avoid potential floor/ceiling

effects for longitudinal analyses; 2) increase the range of cognition measured for more robust correlation analyses with MMN; 3) include Veterans with chronic psychotic disorders so that exploratory analyses can better contextualize similarities and differences between civilian and Veteran studies linking MMN and cognitive remediation performance in chronic psychosis; 4) compare Veterans with and without chronic psychotic disorders in exploratory analyses; 5) see if the utility of measuring MMN at study entry in one type of treatment milieu, if found, translates to other milieus; and 6) ensuring the study achieves its recruitment goals.

We have selected a PositScience/BrainHQ-based cognitive remediation exercise because we have experience with it, have published methodology operationalizing performance on it, and because it is representative of remediation platforms currently available. The PI, mentors, consultants have no real or apparent financial interests in PositScience/BrainHQ, and remain agnostic about which specific remediation programs ought to be most helpful in VA settings.

While we would anticipate a full course of cognitive remediation will improve cognition and potentially improve outcomes, we do not expect the one hour of cognitive training proposed to change cognition or functional outcomes. We have opted to use a one hour of cognitive remediation exercise as opposed to a full cognitive remediation program for several reasons. First, our preliminary data has established that one hour of cognitive remediation is sufficient for MMN to predict treatment response in patients with chronic psychotic disorders. Based on previous studies establishing MMN as a biomarker of general plasticity, we have every expectation that this relationship will generalize to cognitive impairment regardless of mental health diagnosis. However, this has yet to be empirically confirmed. This CDA-2 project will help empirically establish the utility of MMN in predicting gains in cognitive remediation for a heterogenous population of Veterans with mental illness. Second, a full course of cognitive remediation would require 30 hours to complete, placing a strain on the resources and staff at RRTPs/PRRCs. Given the time required for a full course of cognitive remediation (3 months per participant), and the resources afforded by a CDA-2, such a trial would not achieve the sample required to accomplish the proposed Aims. This is particularly salient given that cognitive remediation interventions have been reported to have treatment non-response rates of 20-40%, which we have also found in our published study. Having biomarkers which can better identifying Veterans who will respond to cognitive remediation will justify the resources necessary for a full-scale cognitive remediation trial at RRTP/PRRCs.

Relatedly, in our full cognitive remediation study conducted in a community mental health rehabilitation center, we generated substantial interest from potential participants, and had a fair degree of success in recruitment, but found higher than expected drop out between the start of cognitive remediation and finishing 30 hours (~25% attrition). This first-hand experience has inspired the exploratory aim in order to assess feasibility and acceptability of carrying out a 30-hour cognitive remediation trial in VA mental health rehabilitation settings. I am fortunate to have co-mentors with expertise in implementing and evaluating evidence-based practices for the population with mental illnesses in VA settings (Cohen, Twamley, Marder). Successful completion of this CDA-2 project will help justify a larger rehabilitation trial with more resources so that a full course of cognitive remediation can be effectively implemented and matched to the appropriate Veterans.

2.3.3 RESEARCH PLAN

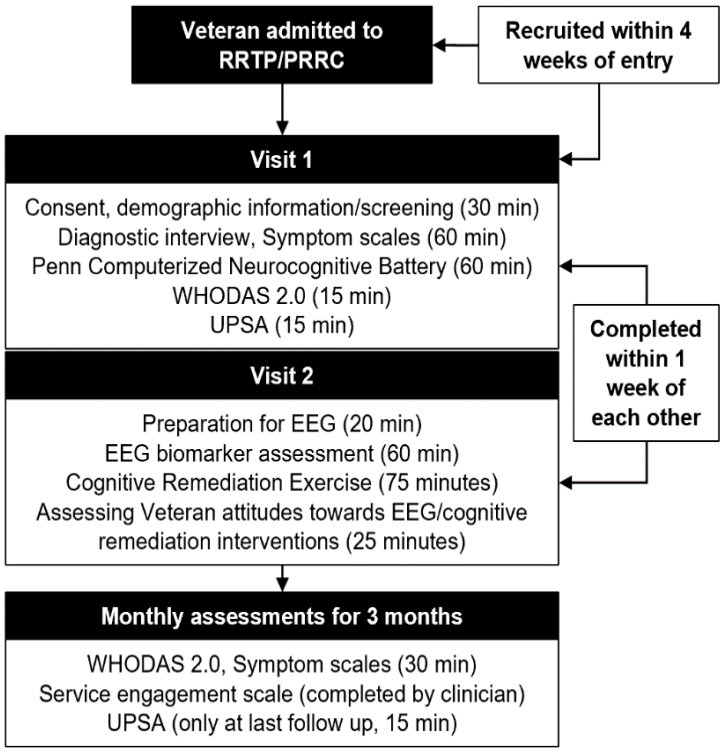
Participants, recruitment, and screening. Veterans who are in their first 4 weeks of receiving services through the VASDHS's RRTP and PRRC will be recruited to participate.

The VASDHS PRRC serves Veterans with psychotic disorders (e.g., schizophrenia, schizoaffective disorder, etc.) with significantly impaired global assessment of functioning (GAF <50). The PRRC Veterans are typically seen at least monthly by a mental health clinician, and engage in recovery coaching, groups and psychotherapy, peer services and supported employment at least twice a month. The VASDHS PRRC has a census of 100 Veterans, with a planned increase in census to ~120 by end of 2019. In FY18 it served 238 unique Veterans. Most Veterans who complete intake stay for >4 months (>90%). The VASDHS RRTP serves Veterans who are currently homeless or at risk of being homeless and who have OEF/OIF service with combat related PTSD. Frequently co-morbid in this cohort are significant mood and anxiety symptoms, and related mood and anxiety disorders. The VASDHS RRTP served a total of 84 Veterans in FY18, with 61 Veterans staying for 4 months or more (>72%). Mental health rehabilitative programming occurs for typically 4 hours a day (groups, psychotherapy, vocational rehabilitation).

In both PRRC and RRTP, an active substance use disorder, active suicidal or homicidal ideation, are exclusionary. Veterans will primarily be recruited to this study via: 1) referral from mental health providers in PRRC and RRTP and 2) advertisements placed in the PRRC and RRTP milieu. Veterans may also self-refer based on word-of-mouth. When Veterans contact study staff to enroll in the study, verbal consent will be obtained to review CPRS for confirmation that the Veteran is enrolled in PRRC/RRTP programming. If the Veteran is eligible and willing to engage, they will be scheduled for an initial session to complete informed consent, undergo screening, and baseline assessments.

Study design, and participant compensation. As shown in Figure 10, after Veterans are referred to the study CPRS is reviewed, we will schedule the Veteran for Visit 1, which includes: informed consent, demographic information, screening (see below), diagnostic interview/symptom scales, cognitive assessment (Penn Computerized Neurocognitive Battery; PCNB), World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0) and UCSD Performance-Based Skills Assessment, brief version (UPSA). At study entry a baseline assessment of treatment engagement will also be collected (Service Engagement Scale, SES; completed by clinician). Visit 1 will be carried out on RRTP/PRRC premises.

Figure 10



In order to provide flexibility in scheduling, Visit 2 may be scheduled up to one week after Visit 1, and include: preparing the Veteran for EEG assessment, EEG assessment, a one hour cognitive remediation exercise delivered on laptop, and an assessment of Veteran attitudes towards EEG assessment and cognitive remediation for the exploratory aim. Visit 2 will be carried out in Dr. Light's laboratory.

Following Visit 2, we will perform assessments of overall functioning (WHODAS 2.0), symptoms, and SES monthly, three times. These visits will be scheduled at RRTP/PRRC premises or Dr. Light's laboratory (based on Veteran preference) in a way that does not disrupt rehabilitation programming. At the last follow up, we will also reassess UPSA.

At the end of study, we will have collected two measurements of UPSA (baseline, month 4), and 4 measurements of WHODAS 2.0 and SES (baseline, months 2-4). We chose 4 months for follow up because based on discussions with PRRC/RRTP leadership, there is significant variability at both milieus about how long Veterans stay in programming beyond 4 months. A shorter time frame will likely not adequately capture usual early drop out, and thus may create spurious relationships between MMN and longitudinal data. A longer time frame for follow up would be preferred, and would be ideal for a larger study/longer award, but not feasible within the bounds of a CDA-2. Characterizing the relationship between MMN and this 4 month longitudinal data will justify larger studies where more distal time points can be assessed.

Visit 1 and 2 are both estimated to take ~180 min (including breaks) each. Follow ups will be ~30 min each, except for the last follow up which will include an additional 15 minute UPSA assessment. Participants will receive $80 for completing Visit 1 and $175 for Visit 2 to limit potential attrition and encourage participation between Visit 1 and Visit 2. They will receive $30 for each follow up meeting, for a final compensation of up to $375 for ~9.5 hours of participation.

Screening. Veterans will be screened at study entry on the following criteria. Inclusion criteria: 1) Veterans must receive services in VASDHS PRRC/RRTP; 2) are within 4 weeks of VASDHS PRRC/RRTP entry; 3) have a DSM-5 mental illness, including schizophrenia, schizoaffective disorder, delusional disorder, MDD, BAD

I or II, generalized anxiety disorder, PTSD verified by Structured Clinical Interview for DSM-5 (SCID-5); 4) Age ≥ 18 years; 5) fluent and literate in English; 6) able to hear 500, 1000 and 6000 Hz tones binaurally at a 45-dB sound pressure level, 7) able to see with an acuity of 20/40 with both eyes tested together (corrected if applicable) by a standard printed Snellen eye chart reading card. Exclusion criteria: 1) active substance use within the last 30 days as determined by CPRS review, self-report, staff report, or positive urine drug screen conducted as part of the screening process; 2) determined by PRRC/RRTP and/or study staff to be at significant risk of exacerbation of symptoms, have acute/ongoing suicidal or homicidal ideation, or other risk due to study participation; 3) Veterans with a history of violence per CPRS review, staff report and study staff judgement; 4) intellectual disability or a major neurocognitive disorder (i.e. dementia).Exclusion criteria are intentionally minimized so that the study sample accurately represents Veterans who utilize PRRC/RRTP services. Up to ~10% of Veterans with mental illness have suicide flags attached to their record (including at the VASDHS PRRC/RRTP). We will not exclude based on presence of a suicide flag as Veterans in both of these milieus have successfully participated in other VA research studies without adverse outcomes.

Sample size and power considerations.
We will recruit 104 Veterans (n=52 in each milieu) to complete Visits 1 and 2 who we will follow for up to 4 months post Visit 1, anticipating a final n = 42/milieu (total final n = 84 across both milieus) accounting for an anticipated attrition rate of 20%.

Power was determined broadly for the two categories of analysis planed. First, analyses that rely on linear mixed-effects models and second for analyses that rely on bivariate regression analysis. For the linear-mixed effects model, power was determined using the methods described by Heddeker et al 1999 [78]. With 2-time points, a medium effect (Cohen's d = .5), reliability of outcome measures equal to 0.7, and alpha of 0.05 (2-tail), n = 43 per group is sufficient for power = 0.8. For the bivariate regression analysis, G*Power (v3.1.9.4) was used to determine that n = 41 per group gives the ability to detect a medium effect size (point-biserial correlation of 0.3) using an alpha of 0.05 (2-tail) with power of 0.8. Based on these power calculations, a final n=42 completers/site was determined to be sufficient for analyses below.

Demographic information to be collected. Age, sex, ethnicity, education history, current medication list, medications taken with in the last 24 hours, nicotine product use/smoking status (and amount if applicable), service connection (yes/no and percent), medical history/diagnoses, housing status, current employment (yes/no; number of hours; place of employment) or most recent employment, weeks worked within the last 12 months will be collected.

Anticholinergic medication burden will be calculated by using the Anticholinergic Cognitive Burden (ACB) scale as previously reported in Joshi et al., 2019[79] for use in Specific Aim 2.3. Briefly, the ACB scale is an empirically derived instrument which assigns risk to medications with anticholinergic properties with potential for cognitive impairment. Medications on this scale are rated from 0 (no known risk for cognitive impairment) to 3 (high risk for cognitive impairment). An individual's total ACB score is the summed from ACB ratings for all individual medications a patient is taking. Measures of anticholinergic burden have been described to affect cognitive functioning and reduce gains from cognitive remediation.

Symptom scales. The following scales will be used to assess current symptoms: mood (PHQ-9; Patient Health Questionnaire-9[80]), anxiety (GAD-7; General Anxiety Disorder-7[81]), trauma (PCL-5; PTSD Checklist for DSM-5[82]), psychosis (BPRS; Brief Psychiatric Rating Scale[83]). These ratings scales are selected for this study due to the fact that these measure are already widely utilized VA-wide (PHQ-9, GAD-7, PCL-5), or are already utilized for tracking PRRC milieu outcomes (BPRS).

Assessments.
Functional assessment. All subjects will undergo the UCSD Performance-Based Skills Assessment, brief version (UPSA) at study entry and 4 months[84]. The UPSA takes ~15 min to complete. The UPSA incorporates role play to assess functional capacity in four broad domains: planning recreational activities, finances, communication and transportation. Raw scores on each subtest are transformed into a standardized subscale scores (0-25), which are summated to an overall score (0-100). The UPSA is widely used for various neuropsychiatric illnesses and in multiple contexts. Using the UPSA will provide an object measure of functional disability.

Psychosocial recovery. All subjects will complete the World Health Organization Disability Schedule 2.0 (WHODAS 2.0) at study entry, and on monthly follow up[85]. The WHODAS 2.0 is an assessment instrument that is designed to be used across both healthy subjects and those with neuropsychiatric illnesses, produces standardized disability levels and profiles, applicable across cultures, in all adult populations and is directly linked at the level of the concepts to the International Classification of Functioning, Disability and Health (ICF). WHODAS 2.0 is composed of 12-item patient-rated measure using a 5-point Likert scale focusing on six domains: cognition, mobility, self-care, getting along with people, life activities, participating in society. The WHODAS 2.0 has been recommended by the DSM-5 Task Force committee to take the place of the global assessment of functioning (GAF) found in previous iterations of DSMs due to the WHODAS conceptually unlinking functional impairment from etiology and weakness of GAF as a construct, especially questionable psychometrics in routine practice[86]. The WHODAS 2.0 12-item takes <15 min to complete.

Treatment engagement. Treatment engagement will be measured using the Service Engagement Scale (SES), a 14-item clinical-rated measure using a 4-point Likert scale that focusing on patient availability, collaboration, help-seeking, and treatment adherence[87]. SES will be completed on a monthly basis by staff at RRTP and PRRC (including at baseline). The SES has been used in usual practice settings and whose psychometric properties have been studied with strong results. At both milieus, four clinicians (psychiatrists, psychologists, nurses, LCSW etc.,) who regularly evaluate and treat Veteran participants, will be asked to complete SES (n=4 raters at each site). The same staff will be used longitudinally throughout the study to the extent possible. The SES takes less <10 min to complete. We will train clinicians/staff on anchors on SES during the 1st quarter of the study to standardize assessment. If staff members choose not to participate in SES data collection mid-study we will work with PRRC/RRTP medical/center directors to identify another staff member to participate in this study. We will provide training to new staff who join the study.

Cognition. Cognitive functioning will be assessed via the Penn Computerized Neurocognitive Battery (PCNB) at study entry[88]. The PCNB is a laptop-based assessment which provides measures of accuracy and speed on 9 neurocognitive domains that have been experimentally linked to specific brain systems with functional neuroimaging studies. This battery has been validated for ages 8-84, has been used in healthy subjects as well as those with various neuropsychiatric illnesses, and has been employed in large-scale genomic and imaging studies. The PCNB is designed to take ~ 1 hour to complete and includes tests to measure the following domains: abstraction and mental flexibility, attention, working memory, episodic memory (word, face, spatial recognition), language reasoning, spatial processing, sensorimotor, motor speed, and emotion identification. Results are reported as individual domain age- and gender- corrected z-scores. These individual scores can be combined to yield global age- and gender- corrected z-scores to allow easy comparison to normative data. The PCNB has high reliability, with item consistency having high Cronbach alpha coefficients, with moderate-to-high within domain inter-item correlation, and low-to-nil correlation between domains.

EEG data acquisition. Veterans will undergo EEG testing, similar to our previously published studies using a 64 channel BioSemi ActiveTwo system[31, 43, 69, 72, 73, 77]. Electrodes will also be placed on mastoids and nose for referencing, and electrodes above and below the right eye at the outer canthi of both eyes will be used to record vertical and horizontal electrooculogram data and to correct EEG for eye movement and blink artifacts. Participants will be viewing a silent movie and instructed to ignore auditory stimuli and that they may be asked questions afterwards. Auditory stimuli will be presented to participants at 85 dB via Etymotic ER3-A insert earphones. Participants will be presented with 1 kHz 85-dB stimuli with a 1-ms rise/fall, with a 500 msec stimulus onset asynchrony, of which 90% are standards (50 msec) and 10% are duration deviants (100 msec), presented in pseudorandom order with a minimum of 6 standard stimuli presented between each deviant. EEG data will be continuously digitized at a rate of ~2.0 kHz and down sampled and referenced off-line (see below). Recorded voltages at analog-to-digital conversion for each electrode site were made relative to a common mode voltage based on the ActiveTwo's CMS/DRL feedback loop. In order to get sufficient data for exploratory analyses, the total recording time will be ~45 min. The total time allotted to EEG acquisition will be ~60 min, accounting time takes to remove EEG electrodes, EEG cap, and for Veterans to clean hair etc., if necessary.

Cognitive remediation exercise. We will use a one hour laptop-based cognitive remediation exercise as we have previously published[77, 89]. Participants will complete the exercise "Sound Sweeps" from the suite of cognitive remediation exercises included in the PositScience/BrainHQ platform. This exercise will be used

because our group has found MMN robustly correlates with cognitive performance on this exercise (see above, preliminary data). Participants listen to a series of two successive tone sweeps (varying in frequency and range and interstimulus interval), and then indicate with two corresponding button presses wither the frequency increased or decreased within each tone. This exercise contains 15 stimuli sets composed of combinations of base frequency (0.5, 1.0, and 2.0 kHz) and duration. Participants must first complete stimulus sets with longer-duration stimuli by demonstrating sustained successful performance at short ISI (i.e., 20 msec) before stimuli sets within shorter-duration stimuli are made available. Auditory exercises are psychophysiologically adaptive: parameters within each stimulus set require a participant to maintain 80% correct performance when established, and task difficulty increases or decreases systematically and parametrically with performance changes. After completing a brief practice block to ensure that participants understand the task, they will engage in three 20-min blocks separated by 5 min breaks. These exercises have been tolerated by all subjects we have tested so far, which include subjects with and without neuropsychiatric illnesses.

Cognitive remediation exercise performance. Each subject's performance will be monitored by recording the number of stimuli sets (measured as a percentage of all available stimuli sets) that are completed over training. Higher values indicate the subject reliably advanced through more of the stimuli content of the exercise (i.e., became proficient on trials with shorter frequency-modulated sweep durations), while lower values indicate remaining at easier training levels. Performance will be operationalized via auditory perceptual learning gains for each subject, defined as the mean percentage of improvement in auditory perceptual learning speed on psychophysically smaller threshold differences in tone duration and frequency. We have previously published this methodology as a way to operationalize performance on cognitive remediation exercises (also, described above in preliminary data)[77, 89].

EEG data processing. EEG data processing will be carried out as previously described[31, 43, 50, 69, 73, 76, 77]. For primary MMN analyses, continuous EEG data will be parsed into 600-ms epochs (−100 to 500 ms) for each stimulus type. After independent component (IC) analysis artifact reduction and baseline correction (−100 to 0 ms prestimulus baseline), EEG epochs containing amplitudes exceeding ±75 μV in any frontocentral electrode (F3, Fz, F4, C3, Cz and C4) will be rejected. Event-related potential averages for standards and deviants will be generated separately, and the resultant difference waves will be low-pass filtered at 20 Hz (zerophase shift, 24 dB/octave rolloff) to remove any residual high-frequency artifact, consistent with established methods. Confirmation of polarity inversion for MMN difference waves will be performed at mastoid electrodes sites. MMN amplitude will be defined as the total mean area between 120 and 200 msec in the deviant-minus-standard difference wave. For exploratory source analysis, in brief, we will run IC analysis over each subject dataset and find the best-fitting single equivalent dipole model for each IC. To enable group-level analysis, we will use k-means to find clusters of equivalent ICs across subjects based on IC equivalent dipole locations, time course, mean log power spectra, and scalp map, obtaining 20 IC clusters allowing identification of IC source-resolved EEG processes occurring in response to processing of auditory deviance. For extended description of methods related to source localization, please see Rissling et al., 2014[43].

General aspects of data management. Drs. Light and Thomas will provide supervision in creating a secure database in the first quarter of the CDA-2 award period that will be maintained on a secure VA research server using the Velos/REDCap software prior to recruitment. Participant names will be kept separate from data. Veterans will be assigned an anonymous ID number, and a file linking each ID number to Veteran participant will be kept in an encrypted electronic file.

General analysis approach: All analyses will be conducted in the general linear model and mixed model frameworks as relevant for Aims 1 and 2. Consistent with standard recommendations, violations of statistical assumptions will be identified using statistical tests and diagnostic plots. When appropriate, robust standard errors will be used to derive test statistics. Outliers will be detected using Cook's distance. Missing data over time will be handled by analyzing all available data (assuming data are missing at random) and by using full information maximum likelihood estimation, or through multiple imputation of data. Analyses will be conducted using R with the assistance of Dr. Thomas. Linear mixed-effects models will rely on the R 'lme4' package. As needed, latent change score analyses will be conducted using the R 'lavaan' package.

SPECIFIC AIM 1: Determine whether MMN is related to functioning, psychosocial recovery and treatment engagement in VA rehabilitation milieus.

Rationale: Veterans with mental illness that utilize VA RRTPs and PRRCs are vulnerable to cognitive impairment, which predisposes them to poor functioning, limits gains in psychosocial recovery, and reduces ability to make use of programming. Objective biomarkers that can be assessed on intake which can identify which Veterans will eventually benefit or fail to benefit from rehabilitation programming will better help identify a sub-group of Veterans that are at risk for poor outcomes and who could potentially benefit from cognitive remediation. In Specific Aim 1, we seek to understand whether MMN is related to: 1) Changes in performance-based measures of functioning from entry VA rehabilitation programming, 2) Trajectory of self-reported psychosocial recovery in Veterans with mental illness, and 3) Clinician-measured engagement of Veterans with mental illness in rehabilitation programming.

MMN is reported a negative value. A more negative MMN value denotes better information processing. Thus, greater MMN amplitude refers to a more negative MMN value (which is beneficial, indicating better information processing).

Hypothesis 1.1: Greater MMN amplitude measured at study entry will predict improvements in UPSA scores over 4 months in Veterans receiving care in RRTPs and PRCCs.

Hypothesis 1.2: Greater MMN amplitude measured at study entry will predict improvements in WHODAS 2.0 total score at 4 months in Veterans who utilize receiving care in RRTPs and PRCCs.

Hypothesis 1.3: Greater MMN amplitude measured at study entry will predict greater average monthly SES scores in Veterans who utilize receiving care in RRTPs and PRCCs.

Primary outcome/Analysis 1.1: A linear mixed-effects model will be used to predict change in UPSA scores over 4 months from MMN values. The model will include the fixed main effect of MMN, the fixed main effect of time (orthogonal linear contrast coded), and the fixed interaction effect MMN by time. The interaction of MMN and time will uniquely predicted changes in UPSA scores over time. The model will also include random intercepts for subjects. This analysis is similar to predicting change scores from typical, non-mixed regression models, but has the advantage of relaxing certain missing data assumptions as above. A positive interaction term will support the associated hypothesis.

Primary outcome/Analysis 1.2: A linear mixed-effects model will be used to predict change in WHODAS 2.0 total score over 4 months from baseline MMN values. The model will include the fixed main effect of MMN, the fixed main effect of time (orthogonal linear contrast coded), and the fixed interaction effect MMN by time. The model will also include random intercepts for subjects and random slopes for time. A positive interaction term will support the associated hypothesis

Primary outcome/Analysis 1.3: A linear mixed-effects model will be used to predict average monthly SES scores over 4 months from MMN values. The model will include just the fixed main effect of MMN. The model will also include random intercepts for subjects. A positive interaction term will support the associated hypothesis.

Potential challenges and alternative analyses for Specific Aim 1

If no direct relationships between MMN and Aim 1 outcomes are found we will analyze individual subdomains of assessment instruments in Aim 1. For UPSA, WHODAS 2.0 and SES scales we will determine whether changes in individual subdomains scores correlate with MMN. Similarly we will explore whether high vs low MMN values (determined via median split) are associated with change in UPSA, WHODAS 2.0 or SES scores over the course of the study. There is a possibility that relationships between baseline MMN, on the one hand, and UPSA, WHODAS 2.0 and SES scores, on the other, will be biased by regression to the mean artifacts. In addition to the above main analyses, we will fit latent change models to the data using the methods described by McArdle and Nesselroade[90]. Results will be compared to those obtained from the primary analyses described above; this will allow us to determine whether regression artifacts significantly impacted the results obtained. These analyses will be supervised by Dr. Thomas and will be a key aspect of the training (Career plan, Objective 3).

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IRB Protocol Amendment (Version 1.0)

1.0 VASDHS IRB Protocol Amendment (For staff changes other than the PI use the IRB Staff Change Form instead)

v20140917

Principal Investigator:

Yash B. Joshi, MD, PhD

IRB Protocol Number:

H190131

Title:

Optimizing Cognitive Remediation in VA Mental Health Rehabilitation Settings

Protocol Nickname:

Optimizing Cognitive Remediation

Amendment Preparation Date:

10/29/2020

Press Save and Continue

Use the ? to the right for an Amendment Guide

2.0 Amendment Description

2.1 Enter a brief title or reference phrase for this modification

Limit 20 characters, to allow you to easily identify this modification from the list of modifications for this protocol.

Amendment 10-29-20

2.2 Describe all features of the amendment request and the rationale for the change:

There are no changes to study aims.
In the initially submitted grant, inclusion criteria included being within 4 weeks of admission to programming at VASDHS's psychosocial rehabilitation and recovery center (PRRC) via the CORE Program in Mission Valley or its mental health residential treatment program (RRTP) at the ASPIRE center. Due to COVID-19, the ASPIRE Center is currently operating at 50% capacity due to the COVID-19 pandemic, and CORE program has moved to essentially all virtual care. There is significant and appropriate concern about Veterans in the mental health residential treatment program/ASPIRE Center leaving their residential VA premises mid-treatment to participate in VA research and the move to virtual care is currently felt to reduce the likelihood of Veterans from CORE/ASPIRE Center engaging in the study within the first 4 weeks of treatment exclusively (i.e., 4 weeks may be too restrictive and with substantially lower throughput in screening and enrollment). We do not therefore believe that we would be able to meet study targets by recruiting from CORE and ASPIRE only at the start of their inclusion into their programs within 4 weeks.

In order to meet study targets we will modify and expand our inclusion criteria to Veterans currently engaged in or within 6 weeks after discharge from any VASDHS RRTP, PRRC, VASDHS inpatient mental health treatment, or VASDHS outpatient mental health treatment. Specifically, this modification /expansion would now allow Veterans engaged in or recently discharged from VASDHS's Substance Abuse Residential Rehabilitation Treatment Program (SARRTP), Veterans who are discharged from 2 South

inpatient treatment, and Veterans who are currently enrolled in outpatient mental health treatment to participate in this study.

This modification will impact only one consideration in terms of inclusion criteria. As initially submitted we had written in our protocol that inclusions criteria required having a DSM-5 mental illness of schizophrenia, schizoaffective disorder, delusional disorder, major depressive disorder, bipolar affective disorder I or II, generalized anxiety disorder or PTSD verified by the structured clinical interview. We would modify this diagnostic inclusion criterion to also include the presence of a substance use disorder (i. e, alcohol use disorder, cannabis use disorder, stimulant use disorder, opioid use disorder, etc.) given that we will be also recruiting from the SARRTP milieu. We will not change our requirement that Veterans would be excluded from the study should that have active substance use within the past 30 days, given that successful completion of SARRTP treatment involves 28 days of sobriety. We will still utilize CPRS review, self-report, staff report or positive urine drug screen conducted as part of the screen process to exclude for active use.
We will not alter our target sample size inclusion, and still plan to recruit 104 Veterans in total, with a final total n = 84, accounting for planned attrition. Since we are including more milieus/treatment settings in the study with this modification, we will also include/recruit clinicians/staff from these settings in our focus groups for our exploratory aim.

In the initially submitted grant, we had utilized the following structure: ~ 3 hour Visit 1 (getting informed consent, demographics, structured interview, symptom scales, cognitive assessment, functional assessments), followed by ~ 3 hour Visit 2 within 1 week of Visit 1 (EEG biomarker collection, 1 hr of cognitive training, assessing Veteran attitudes towards EEG/cognitive training), followed by three monthly assessments of functioning (either in person or on the telephone). This was designed to minimally interfere with Veteran rehabilitation/recovery program.
Given our modification to study recruitment above, this modification to the study structure will be as follows: Visit 1 will be ~7 hours with several breaks and breaks for lunch and include getting informed consent, demographics, structured interview, symptom scales, cognitive assessment, functional assessments, EEG biomarker collection, 1 hr of cognitive training, assessing Veteran attitudes towards EEG /cognitive training. This will be followed by three ~monthly assessments of functioning via telephone. This will reduce burden on Veterans (they will be making 1 in-person trip, instead of 2 in-person trips), reduce attrition between our initially proposed Visit 1 and Visit 2 and also reduce potential risk of COVID-19 associated with participation in the study (to the degree that more trips and contacts between Veterans and study staff would nominally increase already present COVID-19 risk in the community).
Our initial study called for assessment of the UCSD Performance-Based Skills assessment, brief version (UPSA) to be given at study enrollment, and at the last monthly follow up. Given our project modification, we will not collect UPSA as it would not be scientifically relevant/appropriate to all Veteran participants.
Given the changes to study recruitment and structure, we will make the following scientifically trivial changes to account for the new study structure above:
1) Instead of the Penn Computerized Neurocognitive Battery (MCCB), we will use the MATRICS Cognitive Consensus Battery (MCCB) to assess cognition. These cognitive assessments take similar times to complete. This will result in no additional time burden
2) Given that not all Veteran participants will be participating in a mental health rehabilitation setting when enrolling, we will not carry out the Symptom Engagement Scale. In its place, we will assess recovery via the World Health Organization Quality of Life (WHOQOL-BREF). This will result in no additional time burden.
3) We will include the Positive and Negative Symptom Scale (PANSS) for Veteran participants with schizophrenia/schizoaffective disorder. The PANSS is widely regarded to allow for better cross-study comparisons. Administering PANSS will result in a minimal additional time burden.
4) We had initially proposed utilizing the Structured Clinical Interview for DSM-IV (SCID-5) to assess diagnoses. We now propose to use the Mini International Neuropsychiatric Interview (MINI). These are similar assessments, both equally valid. We are making this change due to ease of use. This will add no additional time burden.
5) We had initially proposed using audiology thresholds to determine inclusion and exclusion into the study. We will add two additional measures of auditory fidelity, the Words-in-Noise test, and the Quick Speech in Noise (QSIN) test to help better characterize contributions from hearing problems. This will add ~10 min to the test day.
In addition, we are removing Amy Cohen, Ph.D, who was listed in the protocol as one of the Other VA Collaborator(s). Dr. Cohen is no longer with the VA.

We are attaching revised consents (patient and staff) to reflect these changes. We have also revised the recruitment flyers (Veterans at the ASPIRE Center, Veterans at the CORE Clinic, and staff) and included 3 new flyers (Veterans recently discharged from inpatient facilities, Veterans in outpatient programs, and Veterans discharged from SARRTP). Other attachments, such as the Intrinsic Motivation Inventory (IMI) and Veteran Interview Script, which were part of the approved protocol, will remain unchanged.

2.3 What is the anticipated impact of this amendment on the risk-benefit ratio? (If none, indicate "none")
.

none

2.4 Is re-consenting (or providing new information to) previously consented subjects needed?

○ Yes ◉ No

Explanation for the above:
(If YES, is it reconsenting or just providing information, why, and how it is accomplished)
(if NO, why is it not needed)

No subjects have been enrolled yet

2.5 Is an expedited amendment review appropriate? [i.e., The changes do not affect the assessment of the risks and benefits of the study by substantially altering any of the following: research aims or methodology, nature of subject aprticipation, level of risk, proposed benefits, participant population, qualifications of the research team, or the facilities available to suppor the safe conduct of the research.] See ? for more information regarding requirements.

◉ Yes ○ No

3.0 Requests for Expedited Review

3.1 Please indicate which expedited amendment justification applies:

This human protocol was previously approved under the expedited review process. The research continues to pose no more than minimal risk to human participants and the modifications do not involve any procedures that do not meet the expedited review categories.

○ Yes ◉ No

The research protocol was not originally approved by an expedited review process, but the modifications do not pose an increased risk to participants and the modifications constitute a minor change to previously approved research.

◉ Yes ○ No

4.0 Amendment Features

4.1 Select all features that will be amended:

- ☐ Principal Investigator
- ☑ Protocol Application (research plan)
- ☐ OnRAMP forms (e.g. safety, data security, suicidality, abstract)
- ☑ Informed Consent Form
- ☑ Uploaded documents (e.g. HIPAA, master protocol, etc.)

5.0 IRB Protocol Application

5.1 Revised IRB Protocol Application

Edit/ View	Version	Title
	1.5	Human Protocol (Version 1.5) - Attached

6.0 Consent Form

6.1 Attach any revised consent forms

Version	Title	Category	Language	Expiration Date	Consent Outcome	Checked Out	View Document
1.5	Staff Consent - no HIPAA (stamped)		English				
1.0	Veterans consent with HIPAA revised		English				

7.0 Add/Revise Uploaded Documents

7.1 Revise or Add Attached Documents

Version	Title	Category	Expiration Date	Document Outcome	Checked Out	View Document
2.1	CORE_Veteran_Flyer2	Flyer /Advertisement				55.96 KB
1.1	Staff flyer	Flyer /Advertisement				54.03 KB
1.1	ASPIRE Veteran Flyer	Flyer /Advertisement				55.78 KB
1.0	Flyer to recruit from SARRTP	Flyer /Advertisement				55.16 KB
1.0	Outpatient flyer	Flyer /Advertisement				55.05 KB
1.0	Inpatient flyer	Flyer /Advertisement				55.06 KB

Department of Veterans Affairs

Office of Research and Development (ORD)

Request for Administrative Project Modification	
Project is funded by:	Rehabilitation R&D (RRD)

Instructions: *The VA principal investigator (PI) should complete this form, sign it electronically, obtain the electronic signatures of site investigators, if required, and email it to the local Research Office. If the ACOS/R supports this request, he/she should sign it electronically, and submit it to the appropriate ORD Service by clicking on the button at the end of the form.*

Check appropriate box(es) on left and follow instructions on right for all the changes that you are requesting. Note: additional documentation may be required per the Criteria and Instructions for Requesting an Administrative Project Modification document.

☑ No-Cost Extension ☐ Cost Extension ☐ Redistribute Funds	• Complete sections 1, 4, and 6 below. • Section 6 must clearly describe the justification for a project extension, additional funds, and/or redistribution of funds, if applicable (amount and timing), and details by site, if multi-site.
☑ Change in Aims, Methods, Key Personnel/Effort, and/or Budget	• Complete sections 1 and 6 below. • Section 6 must clearly describe the proposed change from the approved design, its rationale, and implications for the project in sufficient detail to allow scientific review of the request.
☐ Add/Replace Study Site ☐ Change Site-PI	• Complete sections 1, 2, 3, and 6 below. • Section 6 must clearly explain why an additional or replacement study site is being requested and/or why a change in Site-PI is being requested and how the change will benefit the project.
☐ Change in PI	• Complete sections 1, 2, and 6 below. • Section 6 must clearly explain why a change in PI is being requested. Include a detailed explanation of the new PI's current and proposed involvement in the project, VA eligibility, qualifications to complete the work, and whether the current PI will have any continued role.
☐ PI Station Transfer	• The receiving station completes sections 1, 3, and 6 below. • Section 6 must clearly explain what the PI's role and VA appointment (8ths) will be at the new Medical Center. Provide information that demonstrates resources (e.g. required specialized equipment, animal models, access to relevant patient population, etc.) and personnel at the new station will permit the work to be conducted.
☐ Change in Eighths of PI	• Complete sections 1, 5, and 6 below. • Section 6 must clearly explain why the PI is requesting a change in eighths and implications for the project.

1. VA PI (complete for all types of requests)

Last Name, First Name, Middle Initial, Degree(s)		
JOSHI, YASH, B, MD, PhD MBE		
Telephone	VA email	
	yash.joshi@va.gov	
eRA Grant Number 1IK2RX003395-1	Project Start Date 05/01/2020	Project End Date 04/30/2025
VA Project ID D3395-W		
Project Title		
OPTIMIZING COGNITIVE REMEDIATION IN VA MENTAL HEALTH REHABILITATION SETTINGS		
VAMC Name and Location (City, State)		Station No.
VA SAN DIEGO HEALTHCARE SYSTEM, LA JOLLA, CA		664
Electronic signature of the PI		Date 03/24/2025

2. Proposed PI (if changing PI or adding study site)

Last Name, First Name, Middle Initial, Degree(s)	
Telephone	VA email
Number of VA eighths to be held by PI during the award period	
VAMC Name and Location (City, State)	Station No
Electronic signature of proposed PI/Site-PI	Date

3. New VAMC (if transfer of station or adding new study site)

VAMC Name and Location (City, State)	Station No.
Location of research space for this study at the new VAMC	
ACOS/R Last name, First Name, Middle Initial, Degree(s)	
Electronic Signature of the new VAMC ACOS/R (By signing this form, the ACOS is affirming that all VA requirements regarding the conduct of VA research for this study will be met (e.g. appropriate committee approvals).)	Date

4. Project Extension

New end date requested	Total amount, if additional funds are requested
04/30/2026	$ 0.00

5. Change in Eighths of PI

Current Eighths	Requested Eighths

6. Explanation or Justification (see page 1 for required information)

We are submitting this project modification to request: 1) a no cost extension until 4/30/2026 to ensure adequate time to analyze results to complete the project; 2) a minor change related to the Exploratory Aim to remove VA staff interviews which are redundant; and 3) an update to a sub-hypothesis related to Aim 1 based on a previously approved recruitment modification. There are no changes to study personnel or study budget. No redistribution of funds are requested. The modifications do not change the scientific focus or merit of the study, or impact expected deliverables, or alter the expected benefit to VHA.

Below we provide additional detail on each request:

1. No Cost Extension to 4/30/2026.
Despite the COVID pandemic, multiple staffing delays, the PI's parental leave, the project was successfully able to reach end points in a meaningful way to support valuable results and publications. This study included Veterans coming in for an initial visit in-person (Aim 2 outcomes collected at this time point), with three telephone visits assessing symptom ratings monthly (Aim 1 endpoints). Our goal was to consent 104 Veterans, and we expected 20% attrition to generate data for n=84 Veteran for both Scientific Aims 1 and 2. We consented 100 Veterans (96% of target), and for Aim 1 have 80/84 Veteran data (95% of target as of 3/19/2025). For Aim 2, we have exceeded our targets, currently at 86/84 (102% as of 3/19/2025). We have already completed the Exploratory Aim, publishing one paper and are currently in the process of submitting another manuscript. We request this no cost extension so that we can complete the analyses for Aims 1 and 2. The VA San Diego Mental Healthcare Line has committed to maintaining the PI as a full-time VA physician with 2/8ths (25%) protected time dedicated to research to continue this research activity beyond 4/30/2025. At this level of effort we expect analyses to be finalized and the study fully completed by 4/30/2026.

2. Modification to Exploratory Aim.
In the original proposal, the Exploratory Aim sought to interview Veterans and VA staff to better prepare for the “next step” in implementation the project idea and to secure a future Merit grant to support it. A further project modification in 2021 extended this to test a full course of the intervention in a short pilot in support of a future Merit. As noted above, we have already reported on Veteran attitudes in implementation. Furthermore, since the CDA2 was originally proposed, 1) our clinical services have been reorganized at VA San Diego, and the PI and his clinic has already become better integrated with recovery/rehabilitation staff which would be

ACOS/R Last name, First Name, Middle Initial, Degree(s)

Afari, Niloofar, PhD

Electronic Signature of the current VAMC ACOS/R (By signing this form, the ACOS is affirming that all VA requirements regarding the conduct of VA research for this study will be met (e.g. appropriate committee approvals).)	Date
	03/25/2025

7. ORD Decision (for Central Office use only)		
◯ Approved ◯ Disapproved ◯ Partial Approval		
Name	Title	
Electronic Signature		Date
Comments		

Electronic signatures are preferred, but a scanned copy will be accepted.

To attach the required documents, compile them into a single pdf and attach as follows:
(1) from the Main Menu, select View > Comment > Annotations to open the Annotations sidebar;
(2) click on the Attach File icon (paperclip with a chat bubble) and your cursor will look like a push pin;
(3) click on the box labeled “Attach pdf in this area” and the Add Attachment file browser will open;
(4) select the file you want to attach and click on Open;
(5) File Attachment Properties dialog box will open, verify paperclip icon is highlighted, click OK to continue;
(6) the attached file will appear as a paperclip icon.

Email a signed version of this form with the required attachments either using the appropriate submit button below or send directly. Note: pdf email attachment will not be openable while email is composed, but the attachment will be valid once sent.

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Submit this form via email to HSR&D vhacohsrdpm@va.gov

Submit this form via email to RR&D rrdreviews@va.gov