Neuroplasticity in TBI and Schizophrenia

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A. Research Plan

Veterans with cognitive deficits represent a substantial service and financial burden at the Veterans Administration (VA). Importantly, even with treatment, these Veterans have severe problems with community integration[1, 2], defined as the ability to return to full participation in major life roles including competitive employment, school, and supportive social/family networks. Two prominent patient groups within the VA with cognitive deficits and poor community integration are schizophrenia (SCZ) and traumatic brain injury (TBI). SCZ and TBI are common, devastating conditions among Veterans and require high levels of VA healthcare and disability resources. The average annual treatment cost is $31,000/patient with SCZ [3] and three times as high for Veterans with TBI compared to those without [4]. While SCZ and TBI differ in terms of etiology and clinical presentation (SCZ is considered a neurodevelopmental disorder [5] while TBI is acquired), the determinants of poor community integration are overlapping in the two disorders: *both share features of social [6] and non-social cognitive deficits[7, 8], which are both highly related to poor community integration[9-11]. Most of the research on connections to community integration has been done in SCZ and the associations are generally stronger for social cognition than non-social cognition [12].* Evidence indicates that neuroplasticity impairments underlie cognitive deficits in both SCZ and TBI. This SPiRE aims to examine neuroplasticity in these two disorders using novel neurophysiological measures and to evaluate the statistical properties of those measures in each patient population, a necessary step for determining whether they are suitable for assessing individual differences and to serve as biomarkers in future treatment studies.

A1. Neuroplasticity: Neuroplasticity is defined as the malleability of neural organization in response to both endogenous experiences (e.g., cognitive functioning, emotions) and exogenous experiences (e.g., neurostimulation using electricity or magnetic pulses, pharmacological agents). Neuroplasticity is typically studied on two different time frames: short term potentiation (STP), which is the transient facilitation or depression of synaptic activity posited to underlie processes such as sensory adaptation on the order of seconds[13, 14], and long-term potentiation (LTP), which is an enduring structural change of the synapse lasting hours to months. Neuroplasticity is posited to be the neural basis of learning and memory[15].

A2. The relevance of neuroplasticity to SCZ and TBI: There is strong evidence that both SCZ and TBI are associated with impaired neuroplasticity[16, 17]. Dysfunctional neuroplasticity is implicated in SCZ patients' cognitive deficits[18]. Animal models demonstrate that impairments in neuroplasticity are present after injury in TBI[17]. Neuroplasticity, including both STP and LTP, is thought to be mediated by *N*-methyl-D-aspartate (NMDA) receptors. One of the leading neurochemical hypotheses of schizophrenia is that it involves NMDA receptor dysfunction[19], with NMDA antagonists (e.g., ketamine) inducing schizophrenia-like symptoms in healthy individuals[20]. In TBI, alterations of the NMDA receptor after trauma are thought to lead to excitotoxic damage[21] and subsequently impaired neuroplasticity. These findings implicate NMDA-mediated neuroplasticity in both SCZ and TBI. While the NMDA system may be involved in both disorders, we do not know if the same or different mechanisms contribute to dysfunctional neuroplasticity. New treatments that target the root causes of cognitive deficits in SCZ and TBI would be highly valuable for VA's efforts to promote interventions in these Veteran populations. Correspondingly, it is critical to develop objective outcome measures to evaluate the efficacy of such interventions. The current proposal addresses this critical treatment development prerequisite by building on our work with non-invasive EEG paradigms designed to assess neuroplasticity *in vivo*.

A3. EEG assessments of neuroplasticity: STP can be assessed reliably with auditory mismatch negativity (MMN), an EEG response to a "deviant" stimulus that interrupts a stream of identical stimuli[22]. MMN deficits have been well-documented in patients with SCZ[23] and have been linked to deficits in non-social cognition, social cognition[24] and daily functioning[25]. However, much less is known about MMN in people with TBI. Only three studies have been published and the findings are mixed (one showing a deficit, one showing normal response, and one showing increased MMN compared to healthy controls)[26-28]. "Traditional" MMN paradigms have been used extensively in SCZ; recently there has been work on optimizing the methods to better assess STP by using a "roving" type of MMN paradigm, in which the deviant stimulus becomes the standard stimulus until the next deviant which in turn becomes the standard. By varying the number of repetitions before a deviant, one can examine the capacity to encode new information via STP-related processes. As the number of repetitions increases, the slope (or strength) of the MMN also increases, reflecting STP[29]. The roving MMN has rarely been used in SCZ[29-31] and never in TBI, making this a novel area of exploration.

LTP assessments were previously limited exclusively to animal models or excised cortical tissue from humans[32]. However, non-invasive methods for assessing LTP-like plasticity in humans have recently been adapted by our lab and others[30, 32, 33], and they have begun to be applied to clinical populations such as SCZ and depression. These methods focus on visual plasticity and assess EEG responses before and after modulation using high-frequency visual stimulation (HFS) or, alternatively, using extended repeated exposure, which mimics electrical tetanization used in animal or cellular studies. EEG responses after modulation are larger in amplitude, demonstrate the LTP hallmark of input specificity (i.e., only responses to the same stimulus

used in HFS are enhanced), and last for up to an hour[31, 32]. To date, there have been only four published papers examining LTP-like plasticity before and after visual modulation in SCZ[30, 32-34], and only two of these examined patient-control differences[32, 34], with results showing deficits in SCZ. *While there are few studies, correlations between plasticity measures and non-social cognition have been reported in SCZ [33, 35] and HC [36].*

A4. Neuroplasticity treatment applications for SCZ and TBI: TBI and SCZ are both characterized by broad cognitive impairments *(including both non-social and social cognition)* determined by multiple factors and are related to community integration. While we can measure cognition and community integration very well, we do not yet have a full understanding of the root causes of these impairments. We know that neuroplasticity is a fundamental brain process that underlies important *non-social functions such as learning and memory, and social cognitive* functions, such as *emotion and facial affect processing*. Thus, it is a very attractive area for clinical investigation as it provides a basic mechanistic understanding of the root causes underlying cognitive dysfunction in TBI and SCZ, at cellular and neural levels. Altered neuroplasticity can potentially explain a wide range of cognitive deficits affecting the daily functioning of Veterans with these conditions.

It is clear that current treatments are limited and do not lead to functionally meaningful improvements for most patients. To make progress in treatment development, we need to identify clearly specified treatment targets that are amenable to direct intervention. Beyond providing insights into the nature of cognitive impairments in these conditions, this line of investigation can also guide the development of novel neuroplasticity-enhancing interventions for Veterans. New neuroplasticity-focused interventions that improve cognitive deficits, and thereby enhance community integration, in SCZ and TBI will be highly valuable for VA healthcare. Several behavioral and neurostimulation-based neuroplasticity treatments have emerged (e.g., cognitive remediation and transcranial direct current or magnetic stimulation, respectively). To apply and evaluate these methods in SCZ and TBI, it is important to have validated measures of neuroplasticity suitable for use as endpoints in clinical trials to evaluate the efficacy of these approaches. As these potential biomarkers assess neural activity, they provide a more direct (and perhaps more temporally associated) measure of treatment effects than behavioral cognitive tasks. If our results indicate that distinct aspects of neuroplasticity are differentially impacted in TBI vs. SCZ, this would have implications for selective, targeted interventions that address their core deficits. These biomarkers also have broad translational value in animal models for drug development.

B. Innovation, Treatment Implications, and Future Directions

We view this proposal as a necessary first step that will provide innovative insights into neuroplasticity in Veterans with neurodevelopmental or acquired cognitive disorders and will help inform treatment development in future studies. Examining EEG-based measures of neuroplasticity is a small but growing area of research that has not yet been extended to Veterans, except for work by our own lab in Veterans with schizophrenia. Regarding innovation, this would be the first study to examine *in vivo* neuroplasticity measures (both STP and LTP) in Veterans with TBI. Regarding treatment implications, we can use the assessment tools derived from this study to test the effectiveness of plasticity-based interventions, including specialized cognitive remediation or neurostimulation approaches, on improving cognition and community integration in Veterans with cognitive disorders. *It is also possible to use the ERPs to predict treatment response; for example, MMN has been shown to predict treatment response to cognitive remediation in SCZ [37].* Our VA Research Enhancement Award Program (REAP) on Community Integration in Homeless Veterans (M. Green, PI) has shown that SCZ and TBI are major risk factors for homelessness and barriers to community reintegration among Veterans. A novel future direction could extend our assessments of and treatments for neuroplasticity to homeless Veterans. Finally, we could examine physiological factors that influence plasticity biomarkers derived from this study. For example, evidence shows that abnormal neuroinflammation, seen in both SCZ[38] and TBI[39], impairs plasticity and cognition in animals[38]. Examining how neuroinflammation and neuroplasticity interact in Veterans with these disorders would be highly informative and point to anti-inflammatory treatments to improve plasticity and cognition.

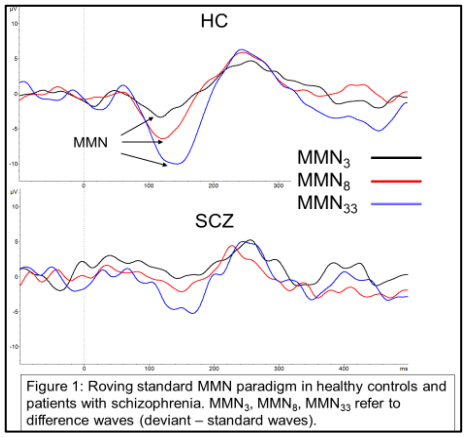

Figure 1: Roving standard MMN paradigm in healthy controls and patients with schizophrenia. MMN_3, MMN_8, MMN_{33} refer to difference waves (deviant – standard waves).

C. Preliminary Studies

A focus of our lab has been to examine determinants of functional outcome and community integration in Veterans with SCZ and other serious mental illnesses using self-report, clinical interviews, behavior, EEG, and neuroimaging. Our work in SCZ demonstrates that the PI and research team are qualified to conduct the proposed research in Veterans with TBI, given the similar disturbances in cognition and functional outcome. In this section we discuss our EEG studies of neuroplasticity in Veterans with SCZ. The goals of this SPiRE are to examine neuroplasticity in SCZ and TBI using novel EEG methods, to provide an objective biomarker to assess neuroplasticity, and to understand how determinants of outcome (e.g., cognition) are related to neuroplasticity.

Roving mismatch negativity (rMMN): We recently published a study examining the relationship between MMN and auditory hallucinations in SCZ[40]. This study utilized one version of the roving MMN paradigm that is proposed in the current application (see **D5** below). In our study, we found that the ERP response to the deviant increased in amplitude as the number of standards presented increased, reflecting STP. However, this increase in STP was significantly smaller in SCZ than in healthy controls (Figure 1).

Long-Term Potentiation (LTP): Our lab recently published on EEG-based measures of LTP *in vivo* in Veterans with SCZ and healthy controls[30]; this was only the third such study published in this population. As discussed in **Section A**, LTP is assessed in this paradigm by comparing visual evoked potentials before and after HFS. We performed t-tests on post- minus pre-HFS difference waves and subjected them to data-driven mass univariate analyses (correcting for the vast number of comparisons) to identify time windows and electrodes with clear signals (Figure 2). The difference waves are plotted as topographical maps; in the raster plot, significant post-pre HFS differences at each time sample and electrode are shown in blue, demonstrating significant LTP between 140-227 ms over parieto-occipital electrodes 2 minutes after HFS. We utilized the same paradigm in the only other paper examining SCZ-control differences in LTP[32]. However, more recent paradigms have been developed with improved features, such as the ability to evaluate input specificity and longer time frames for LTP assessment, so we will use a newer approach in the current study (see **D5**).

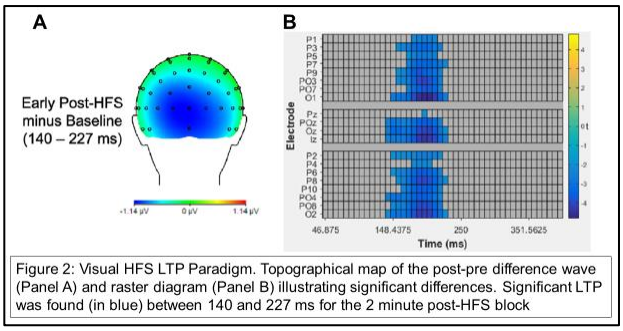

Figure 2: Visual HFS LTP Paradigm. Topographical map of the post-pre difference wave (Panel A) and raster diagram (Panel B) illustrating significant differences. Significant LTP was found (in blue) between 140 and 227 ms for the 2 minute post-HFS block

D. Research Design and Methods

D1. Study Overview: This is a 2-year study to assess EEG-based biomarkers of STP and LTP in Veterans with (either SCZ or TBI) or without (healthy Veterans) cognitive disorders. This study will leverage three aspects of existing research infrastructure at the GLA: 1) the VISN 22 MIRECC (laboratory assessment space, interviewer training); 2) the MIRECC Data Core (statistical and data management/quality assurance support); and 3) the REAP (Director: Michael Green, Ph.D.). These are fully described in the **Resources** section. Institutional Review Board (IRB) and start-up activities, including creating a secure on-line data entry and storage system with the Data Core, will be accomplished in the first quarter of the study. Recruitment will continue up through Q3, Year 2. Q4 of Year 2 will focus on data analysis, dissemination through scientific presentations and publications, and preparation of a MERIT application.

Table 1: Timeline of Activities (per quarter of project)

	Year 1				Year 2			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Startup	■							
Recruitment and Data Collection (n = 12-13 per quarter)		■	■	■	■	■	■	
Analysis, Write-Up, MERIT Application								■

D2. Participants and Recruitment: We will recruit 25 participants in each patient group and 25 healthy Veterans (total N = 75). The groups will be comparable on key demographics (i.e., parental education, gender). Veterans with SCZ will be recruited from the GLA Psychosis Clinic and our MIRECC Patient Registry. Veterans with TBI will be recruited from the Neurobehavior Clinic (directed by Dr. Mario Mendez, co-I on this proposal), and the Polytrauma Clinic at GLA. Selection criteria for all participants include: 1) age 25-55; 2) no other neurological or medical condition interfering with providing informed consent or valid assessment; 3) not meeting diagnostic criteria for current depression *based on the Structured Clinical Interview for DSM-5 (SCID-I)[41] or depressive symptoms rated moderate or higher (a rating of 13 or higher on the Hamilton Depression Rating Scale [42])*; 4) no DSM-V substance use disorder greater than moderate severity in the past 3 months; 5) *no form of cognitive remediation in the 6 months prior to testing*; *6) an 8th grade reading level assessed with the Wide Range Achievement Test (WRAT [43]);* and 7) normal or corrected-to-normal vision and hearing. The age range was chosen to exclude younger participants whose brain development and plasticity is still occurring[44, 45], and a conservative upper range where age-related cognitive declines may prominently begin[46, 47]. *Exclusion criteria for all patient participants include: 1) changes in medication dosage or type 3 months prior to testing; 2) hospitalization for psychiatric health in the 3 months prior to testing; 3) changes in housing status in the 6 months prior to testing.* Full **inclusion/exclusion criteria** and expected ethnicity/race/gender breakdowns are shown in **Human Subjects.**

Clinical Diagnosis: For SCZ, diagnosis will be made with the SCID-I and information from the medical chart. All interviewers are trained through the Treatment Unit of the VA VISN 22 MIRECC to a minimum kappa of 0.75 for key psychotic and mood items, and a minimum intraclass correlation of 0.80[48]. For TBI, participants will have had a concussive or closed-head injury as identified in a structured TBI interview[49] and meet a mild *(n* =

12) or moderate *(n = 13)* diagnosis of TBI based on criteria adopted by the VA[50]. *All TBI participants must be at least 6 months post injury to be enrolled.* We elected to not recruit participants with severe TBI as this is the most intractable form of TBI, with lengthy hospitalization and extensive rehabilitation. For mild TBI, criteria include evidence of impact to the head resulting in a loss of consciousness (LOC) ≤ 30 minutes with one or more of the following: posttraumatic amnesia, disorientation or confusion, and best Modified Glasgow Coma Scale (GCS)[51, 52] of 13-15 in the first 24 hours after injury. For moderate TBI, criteria include evidence of impact to the head resulting in a loss of consciousness (LOC) > 30 minutes and < 24 hours with one or more of the following: alteration of consciousness > 24 hours, post-traumatic amnesia > 1 and < 7 days, and best GCS of 9-12 in the first 24 hours after injury. Further exclusion criteria for TBI patients include other neurological sequelae (e.g., focal neurological signs or symptoms or evidence of an abnormal computed tomography or magnetic resonance imaging scan). For SCZ, further exclusion criteria include head trauma or injury with LOC (LOC due to other non-concussive injuries lasting < 5 minutes will be acceptable).

D3. Demographic and Medication Considerations: We will use a naturalistic sample of Veterans with TBI or SCZ, which will make the results more generalizable to these disorders. Using a naturalistic sample within the context of the SPiRE mechanism will inform us about how to match groups in future studies. An additional methodological concern is the number and variety of psychotropic medications for those in the patient groups, including antipsychotics, antidepressants and mood stabilizers, stimulants, and anxiolytics. Unfortunately, there is little we can do about the potential concern of long-term polypharmacy, as that is inherent to the two patient groups. We will attempt to partially address potential effects of medications on our dependent variables using the following approach. We will carefully record all information, via self-report and inspection of medical records, about psychiatric medications and examine relationships to the plasticity measures. Sedatives and benzodiazepines, which may affect performance on behavioral and electrophysiological measures, will not be permitted within 12 hours of testing.

D4. Clinical interviews and scales: A comprehensive psychiatric and social history form developed by our lab will be used to record additional information that may be of interest to consider in secondary analyses, such as duration of illness, socioeconomic status, and cigarette smoking status. We will administer the SCID[44] to all potential participants, and the SCID-Personality Disorders[53] to healthy Veterans only. Clinical symptoms for all participants will be assessed with the Expanded Brief Psychiatric Rating Scale[54], the Clinical Assessment Interview for Negative Symptoms[55], the Hamilton Depression Rating Scale[42], the Patient Health Questionnaire[56], the Young Mania Rating Scale[57], PTSD Checklist (PCL-5)[58], and the Addiction Severity Index[59]. These measures will be used to characterize the samples and explore relationships to plasticity.

D5. ERP Recording and Analysis Procedures: ERP recording and processing will use existing equipment in the lab of Dr. Green at the VISN22 MIRECC (see Facilities and Other Resources). Stimulus presentation and EEG data synchronization will use Presentation (Neurobehavioral Systems, Inc, Berkeley, CA). EEG will be collected continuously using a 64-channel BioSemi ActiveTwo amplifier (BioSemi, Germany), sampled at 512 Hz from DC to 100 Hz. Four electrodes to monitor horizontal and vertical electrooculogram will be used to correct for eye blinks and other movements using established methods[60]. Data will be processed with Brain Vision Analyzer 2, EEGLab[61], Mass Univariate Analysis Toolbox[62], and PCA Toolbox[63] using established methods to obtain and analyze ERPs (e.g., [64-66]).

Evaluation of Within-Session Reliability (Internal Consistency): In order to validly use ERPs to make inferences, ERP components must demonstrate acceptable reliability[67, 68]. ERP score reliability provides an estimate of signal-to-noise ratio (SNR). Ensuring adequate reliability is critical when comparing ERP scores from different task conditions, because condition differences can be obscured by low SNR. Similarly, low score reliability imposes an upper limit on correlations with other variables, such as cognitive scores. Hence, poor score reliability can limit effect sizes for both between-condition differences and correlations with other variables. We will use the ERP Reliability Analysis (ERA) Toolbox, which utilizes G Theory-based algorithms to estimate reliability[67]. The ERA toolbox also provides an estimate for the length of a task that is needed to achieve a particular reliability score for all conditions and groups and in this way serves to optimize the length of a task for clinical research. Recent publication guidelines from leading journals require reliability estimates be published and recommend a cutoff of 0.8 for an ERP to be considered reliable.

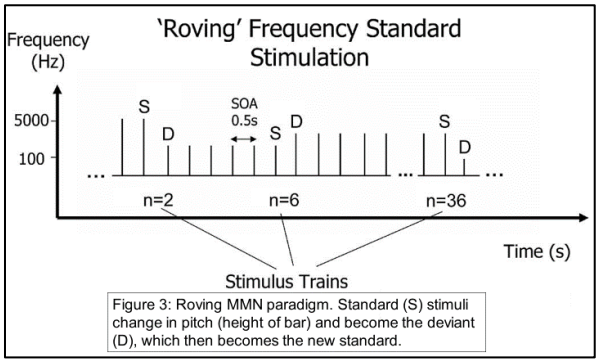

Figure 3: Roving MMN paradigm. Standard (S) stimuli change in pitch (height of bar) and become the deviant (D), which then becomes the new standard.

Short-term Plasticity – Roving Mismatch Negativity (rMMN) (30 min): We will utilize a rMMN paradigm[69] that can assess STP by systematically manipulating the number of standard stimuli that appear before a deviant. The rMMN presents a series of identical "standard" stimuli for a set number of repetitions (i.e., either 2, 6 or 36

times) followed by a “deviant” stimulus (differs in frequency from the standards). With each change in the standard series, the deviant stimulus changes in pitch (in 50 Hz steps between 700-1200 Hz) relative to the preceding series of standards, resulting in distinct auditory stimuli that serve as both standards and deviants during the run. Subjects will ignore the tones and perform a visual attention task (press a button when fixation cross changes contrast) which serves to direct attention away from the tones. A schematic of the paradigm is shown in Figure 3. Stimuli are presented in 4, 5-minute blocks, with a 60 s break after each block. rMMN will be presented in between post-modulation blocks in the LTP task (see below). Auditory stimuli, presented via earphones, consist of 80 dB tones; the interstimulus interval is 400 ms. There are 85 deviant trials in each block. Data will be processed with established methods[40]: segmented (-100 to +500 ms time-locked to stimulus onset), ocular correction[81], baseline correction, and finally artifact rejection. MMN is scored as the mean amplitude between 100-200 ms over fronto-central electrodes (F1, Fz, F2, FC1, FCz, FC2) for the difference between deviants – standards. Plasticity is defined as the change in slope of MMN amplitudes over the change in the number of standards (i.e., difference in MMN amplitude after the most standards (36) and fewest standards (2)), with a larger slope indicating greater plasticity.

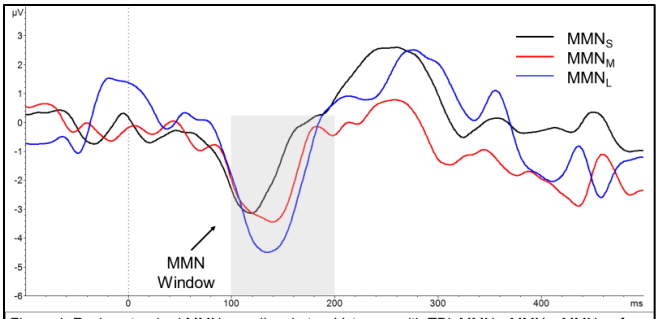

Figure 4: Roving standard MMN paradigm in two Veterans with TBI. MMN$_S$, MMN$_M$, MMN$_L$ refer to difference waves (deviant – standard waves) for short (S), medium (M), and long (L) series of standards.

Feasibility Data: Data from a sample of SCZ patients is presented in **Preliminary Studies**. For TBI, we piloted this task in two individuals to demonstrate valid ERPs can be obtained. Figure 4 shows ERP difference waves after short, medium, and long standard repetitions. MMN can be observed as a negative voltage between 100-200 ms that increases in size in response to larger number of standard stimulus repetitions. These data demonstrate that people with TBI provide valid data in the expected direction, suggesting that this task can be validly administered in the proposed sample.

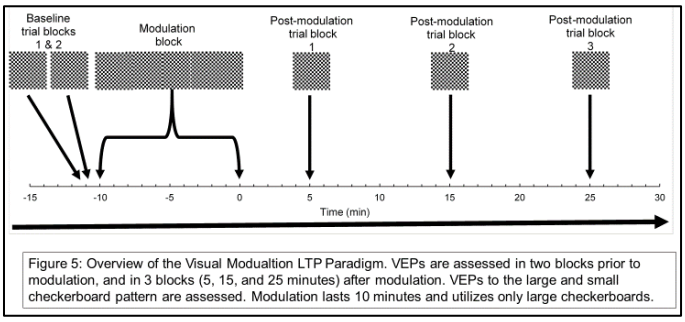

Figure 5: Overview of the Visual Modualtion LTP Paradigm. VEPs are assessed in two blocks prior to modulation, and in 3 blocks (5, 15, and 25 minutes) after modulation. VEPs to the large and small checkerboard pattern are assessed. Modulation lasts 10 minutes and utilizes only large checkerboards.

Long-term Plasticity – Visual Modulation Paradigm: We will assess visual evoked potentials (VEPs) before and after extended exposure (i.e., “visual modulation”) to assess LTP-like plasticity, modeled after [70] and adapted by our lab. Stimuli consist of two different checkerboard pattern stimuli: one comprised of large black and white checks and the other comprised of small black and white checks. Only the large checkerboard pattern will be used in the modulation block; this will be done to assess input specificity (i.e., plasticity should only be seen to large but not small checkerboards). On alternating trials within a block, the checkerboard pattern reverses color (i.e., black becomes white and white becomes black). The checkerboard stimuli include a small red central dot to facilitate gaze fixation. The task includes 2 baseline blocks, 1 10-minute modulation block, and 3 post-modulation blocks occurring 5, 15, and 25 min after the modulation block (Figure 5). Prior to modulation, the large and small checkerboard stimuli are presented in separate (counterbalanced) blocks, for a total of 80 stimuli for each type of stimulus. For the modulation block, only the large checkerboard is presented for a total of 10 minutes (i.e., 1200 reversals). A total of 40 large and 40 small checkerboard stimuli are presented in separate blocks in each of the three post-modulation blocks. All stimuli are presented at 2 Hz.

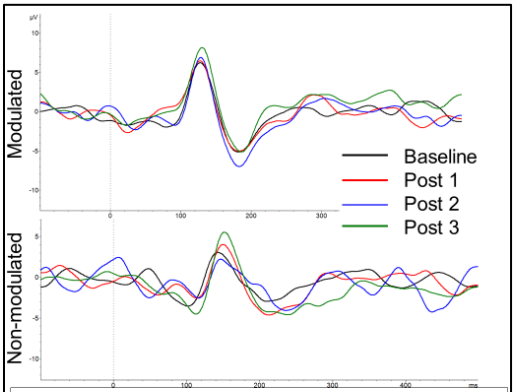

Figure 6: Visual modulation LTP paradigm data in two Veterans with TBI. The P1 (~120 ms) is higher at all three time points in comparison to pre-modulation (baseline) for tetanized stimuli.

We will utilize a data-driven approach to identify time windows and electrodes that show significant differences post-pre modulation [32, 61], focusing on time regions and electrodes overlapping with the early sensory VEPs C1, P1, and N1 that occur between 50-250 ms. Once these are identified, a PCA[63, 71] applied to the original waveforms will be used to isolate ERP components (e.g., C1, P1, N1) falling within time windows showing significant effects. Amplitudes will be calculated for each identified component and used in analyses. This method provides an objective, unbiased method of selecting components that show task-related modulation.

Feasibility Data: Data from a sample of SCZ using a similar paradigm is presented in **Preliminary Studies**. For TBI, we piloted the new task in 2 individuals to demonstrate that valid waveforms can be obtained. Figure 6

shows VEPs recorded before modulation ("baseline") and 5, 15, and 25 minutes after modulation (Post 1, 2 and 3, respectively). The P1 VEP (positive voltage at ~120 ms) increases in amplitude after 10-minute modulation using modulated stimuli (i.e., large checkerboards; top of figure) but not to non-modulated stimuli (bottom of figure). These data demonstrate that people with TBI can perform the task and provide valid data, lending confidence that this task can be successfully used in the proposed sample.

D6. Cognitive Assessments:

Non-social cognition: MATRICS Consensus Cognitive Battery (MCCB)[72, 73]: The MCCB assesses 6 domains of cognitive functioning: speed of processing, attention/vigilance, working memory, verbal learning, visual learning, and reasoning/problem solving. Raw values are converted to *t*-scores adjusted for age and gender. An overall composite score is calculated. Time: 60 min.

Social cognition: Empathic Accuracy (EA) task[74]: The EA task consists of 13 video clips lasting 2.0-2.5 minutes of an individual ("target") discussing a positive or negative experience. After speaking of their experience, the targets provided a continuous rating of how they were feeling. Participants view each video clip and continuously rate how they think the target is feeling. The primary dependent variable is the average correlation between the participant's and target's ratings. Time: 30 min.

Social cognition: Facial Emotion Recognition (FER) task[75]: The FER consists of faces of Caucasian and Asian actors portraying one of 6 emotions (afraid, angry, disgust, happy, sad, surprise) or neutral, drawn from a facial expression stimulus data library[76]. The participant selects the expression they think is correct. Eight trials per expression are shown. The primary dependent variable is the total number correct. Time: 15 min.

D7. Community Integration Measures: We will use three complementary scales: 1) the Role Functioning Scale (RFS)[77], which assesses aspects of work, independent living, and family/social connections; 2) the Lubben Social Network Scale (LSNS)[78]; and, 3) the Community Integration Questionnaire (CIQ)[79]. We have extensive experience with all scales. We will combine the summary scores from each measure to obtain a standardized community integration composite score to be used in analyses. Time: 15 min.

D8. Design Considerations: For this SPiRE, we elected to recruit Veteran with any mild or moderate TBI diagnosis from local VA clinics, rather than selecting based on type (e.g., blast vs. impact, closed vs. open) as the sample will be more representative of our VA. We realize the sample may be heterogeneous, with differences in TBI injury, types/doses of medications (e.g., anxiolytics, antidepressants, stimulants), and in co-morbid diagnoses (e.g., post-traumatic stress disorder, PTSD). Regarding PTSD, we will assess for presence (meeting DSM-5 criteria) and severity of symptoms (i.e., PCL-5) and examine relationships to the plasticity measures. We will include type of head injury in exploratory analyses. Regarding neuroplasticity assessment, we could have used fMRI or alternative EEG methods. We chose EEG as there are no behavioral measures, and EEG is easier to assess and disseminate in VA clinics than expensive and burdensome fMRI. We chose to assess both STP and LTP as they assess different aspects of neuroplasticity: LTP results in changes at the synapse (e.g., alterations in the number and location of AMPA receptors), whereas STP results in transient changes in synaptic activity not due to structural alterations. Group comparisons are not part of this grant or encouraged by this grant mechanism and we will not formally test for them. However, the data may allow us to see differences in patterns that will suggest differences or similarities in underlying mechanisms and relationships to cognition and community integration in the two patient groups. Given the novel and innovative nature of the research questions, as well as the inclusion of two disorders with similar cognitive deficits, the data from this study will be informative in guiding paradigm development and parameters to be used in a larger Merit. The inclusion of healthy Veterans without cognitive impairments will also be beneficial as these plasticity paradigms have rarely, if ever, been used in these Veterans, and we can apply the same questions of tolerability and feasibility to this group to refine future versions of the tasks to be used in larger grants that will examine group differences.

D9. Analytic Plan: Consistent with the SPiRE mechanism, statistical analyses will be more descriptive than inferential. For Aim 1 we will assess whether specific targets are met such that at least 90% of those recruited in each group (a) complete the EEG measures and demonstrate tolerability (based on subject self-report *utilizing a questionnaire developed in our lab; see Appendix 1*); and (b) provide high quality EEG data uncontaminated by noise or artifacts and cleaned via traditional methods (e.g., eye-blink correction, artifact rejection). We will also determine the average number of trials needed and the fraction of subjects who fail to achieve within-session reliability (cutoff of 0.8 for internal consistency), allowing us to optimize the paradigms for future studies. For Aim 2, we will examine the distributional properties of the neuroplasticity measures in each group to ensure that they show sufficient variability to be useful as potential biomarkers, provide estimates of key parameters (e.g., mean, SD), and inform the need for transformations or other specialized analytic approaches. For Exploratory Aim 3 we will use correlational analyses to assess the relationships of neuroplasticity measures with downstream cognitive and functional outcomes as well as demographic and clinical characteristics, *as well as the relationships between the two neuroplasticity measures themselves*.

References

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