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Project Title: Neurophysiology Markers of PTSD's Presence, Severity and Therapy

HUMAN SUBJECTS RESEARCH PROTOCOL

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1.0 Objective and Specific Aims:

This project evaluates novel PTSD biomarkers which are based on measures of coherent activity among the regions of cerebral cortex during sleep. In preliminary studies on EEG acquired during sleep from Veterans with PTSD alone as well as other co-morbidities, we have shown that the neuromarkers were highly sensitive/specific to the presence of PTSD, and highly sensitive to the severity of symptoms in PTSD group.
The overall goal of this project is to further validate these novel neurophysiology markers in retrospective and prospective studies. The Overall hypothesis to be studied is as follows:

Specific Aim 1: Formally establish the sensitivity/specificity of the novel PTSD neuromarkers by analyzing a large existing dataset

Hypothesis 1.1: Neuromarkers can distinguish PTSD from non-PTSD groups with clinically acceptable sensitivity and specificity.

Hypothesis 1.2: In PTSD group, Neuromarkers will strongly correlate with PTSD symptom severity and measures of functional outcome.

Specific Aim 2: Evaluate improvement on the performance of the neuromarkers using a dense array EEG montage [Prospective Study 1]

Specific Aim 3: Evaluate the sensitivity of Neuromarker to the improvements in PTSD symptoms

Hypothesis 2: Neuromarkers will strongly correlate with the improvement of PTSD symptoms

2.0 Background and Significance

2.1 Background

Post-traumatic stress disorder (PTSD) is a chronic and disabling neuropsychiatric disorder that is characterized by severe sleep disturbances, avoidance behaviors, physiological hyper-arousal, and re-experiencing symptoms following exposure to a traumatic event [1]. Epidemiologic studies have shown that nearly 56% of people will experience a psychologically traumatic event and between 7-12% of individuals will meet criteria for PTSD during their lifetimes [2-5]. In the United States military, Veterans have an even higher risk of developing PTSD compared to the

civilian population, with the lifetime prevalence of PTSD estimated at 19% for Vietnam-era Veterans [6]. Similar patterns are observed among OIF/EIF Veterans: Approximately 17% of active duty soldiers and 25% of OIF met criteria for PTSD 3-6 months post-deployment [7].

The current practice for diagnosing of PTSD primarily relies on subjective clinical assessments by the clinicians and patients' self-reports. Subjective evaluation of PTSD symptom severity is also an integral part of the current treatment approaches for PTSD, which includes pharmacotherapy [8,9], prolonged exposure (PE) therapy [10-12], cognitive processing therapy (CPT) [10, 13,14], eye movement desensitization and reprocessing (EMDR) [12,15,16], and stress inoculation training [17,18]. An objective and neurophysiologically-based method for directly assessing brain function is desperately needed to improve diagnosis of PTSD and corresponding assessment of treatment response.

This need is highlighted by the recommendations from the Institute of Medicine, National Academy of Science (IOM-NAS), which conducted a comprehensive assessment of the current PTSD diagnosis and treatment methods and identified potential shortcomings of the current diagnostic and treatment techniques [19]. A major recommendation by the IOM-NAS was to fill the urgent need for development of methods for the more precise and objective diagnosis of PTSD and its severity level, for the objective and faster evaluation of treatment efficacy, and for the ability to predict who might be at risk of relapse.

Rationale and Novel Approach for Developing Neurophysiology Markers for PTSD

A number of neuro-imaging studies using magnetic resonance imaging (MRI and fMRI) and positron emission tomography (PET) have reported altered brain activity in PTSD in the ventromedial prefrontal cortex (vmPFC), insula, amygdala, and hippocampus [20-23]. More recent evidence, however, suggest that abnormal network connectivity and communication is the underlying cause of PTSD. Bluhm et al. [24] reported diminished levels of connectivity between the posterior cingulate cortex and the right frontal cortex as well as the left thalamus in their PTSD group. Sripada et al. [25] reported a decrease in the rostral anterior cingulate cortex/vmPFC, and an increase in the salience network including the amygdala, during resting state MRI study.

Our Approach: Based on the above findings, and supported by strong association between PTSD and sleep disturbances (reviewed in next paragraph), we hypothesized that a neuro-physiologically based marker, derived from dynamic measures of impaired synchronous activity among the regions of cerebral cortex during awake period prior to sleep onset and various stages of sleep, could be utilized for the objective assessment of PTSD presence and severity, as well as a potential predictor of treatment response. We tested this hypothesis by developing markers based on the relative level of coherent electroencephalograph (EEG) between various cortical regions in specific frequency bands and during sleep.

The selection of sleep as the test condition was motivated by the extraordinarily high prevalence of sleep disturbances in individuals with PTSD, to the point that some have proposed that sleep disturbances are a hallmark feature of the disorder [31-42]. Over 70% of civilians and Veterans with PTSD have reported persistent and severe nightmares and disturbed sleep [33].

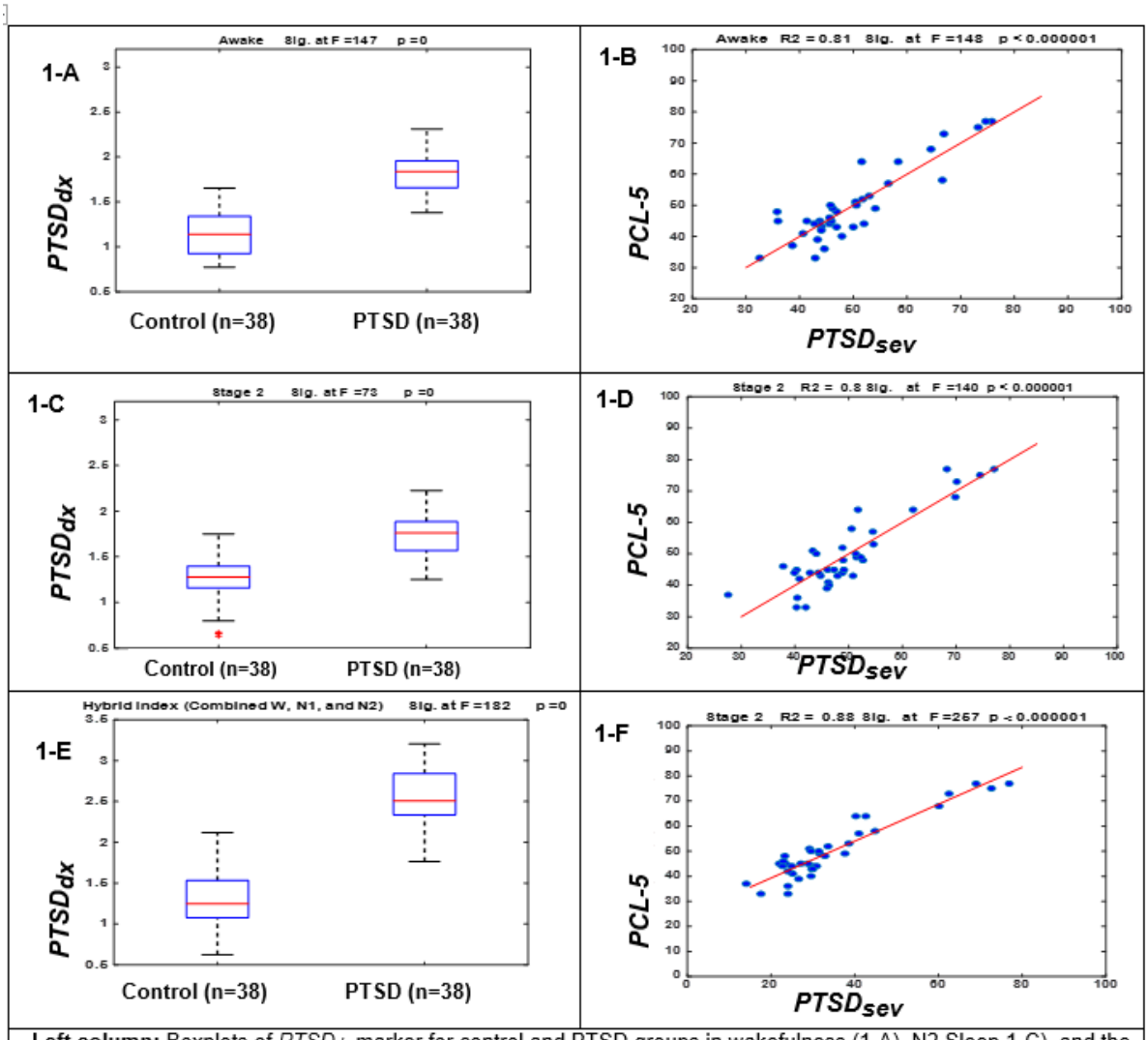
2.2 Preliminary Studies

In preliminary studies on EEG acquired during sleep from Veterans with PTSD alone (n=38), TBI alone (n=30), PTSD and TBI (n=25), and an aged matched no PTSD or TBI control group (n=38), we have shown that a set of neuromarkers were highly sensitive/specific to the presence of PTSD, and highly sensitive to the severity of symptoms in PTSD group.

The PTSD neuromarkers of this project are built from combination of regional brain coherence markers (BCM). BCM computation is based on the levels of coherence and synchronicity between pairs of scalp EEG activity. These coherence values were computed for the entire sleep study using

5-second sliding windows that were overlapped by 1 second. The frequency band spanned from 0.2 Hz to 50 Hz with a resolution of 0.2 Hz. Vectors of BCM were constructed over each of the five stages of sleep study (Awake [W], Rapid Eye Movement [REM], non-REM [NREM] stages N1, N2, and N3). Our analysis showed that the markers computed in awake and stage N2 sleep were significantly different in PTSD than the control group and also produced the highest level of correlation with the PTSD symptom.

The following figure shows the excellent capability of the PTSD diagnostic Neuromarker ($PTSD_{dx}$) and PTSD severity marker ($PTSD_{sev}$) in differentiating Controls from PTSD, and in correlation with symptoms, respectively.



Left column: Boxplots of $PTSD_{dx}$ marker for control and PTSD groups in wakefulness (1-A), N2 Sleep 1-C), and the Hybrid W and N2 (1-E). On each box, the central mark is the median, the edges of the box are the 25th and 75th percentiles, the whiskers extend to the most extreme data-points the algorithm considers to be not outliers, and the outliers are plotted individually

Right Column: Scatter plots of $PTSD_{sev}$ vs PCL-5 in groups in awake (1-B),, N2 Sleep (1-D), and the Hybrid W and N2 (1-F).

2.3 Significance

The goal of this project is to develop a much-needed objective biomarker in PTSD that will allow more accurate treatment choices and faster evaluation of treatment response for Veterans with PTSD. However, current clinical practice is based on subjective assessments and it lacks "objective" PTSD diagnostic and assessment methods based on underlying brain mechanisms of dysfunction. We propose to use quantitative EEG, a non-invasive, cost-effective, totally portable procedure, to precisely measure activity and connectivity between different parts of the brain during awake and sleep states in Veterans with and without PTSD. If successful, these objective neuromarkers can be used not only for more accurate detection of the presence and severity of PTSD, but also for a faster and more accurate evaluation of response to current therapy, informing the potential need to switch interventions, and identifying those at high risk for relapse.

3.0 Research Design and Methods

3.1 Drug/Device Information

For EEG sleep studies of the project, LiveAmp EEG hardware attached to electrode cap (Fig. 1-HS) from Brain Products GmbH, Germany will be used. Such devices are battery-operated and routinely used at the sleep laboratories and patient's home for the clinical/research assessment of sleep and neurological disorders.

Figure 1-HS.Wearable 64 channel EEG sleep device from BrainProducts corp.

3.2 Type of Study

This project consists of three type of studies:

Study 1. This is a retrospective study. At ENRM VA, the Neuromarker analyses will be applied to a large existing database (n=656) containing sleep EEG recordings along with health and functional outcome measures, from Veterans with PTSD only (n=107), TBI only (n=126), both PTSD and TBI (n=87), depression only (n=80), and controls (no PTSD/TBI/Depression; n=256).

Study 2. This is a prospective pilot study at ENRM VA that will be conducted to evaluate potential improvement on the performance of the Neuromarkers using a dense array (up to 64 channels) EEG montage that covers all areas of the brain and with greater resolution, as compared to the original 6-channel EEG protocol. The sample will include up to 25 PTSD and control subjects.

Study 3. This is a prospective study conducted at ENRM VA on a single cohort of up to 55 Veterans with PTSD at multiple times during their ongoing clinical treatment for PTSD at the ENRM VA. Night time sleep EEG measures will be collected at pre-treatment, after first session of therapy, immediately after completion of therapy, and at 3-month post therapy. Measures of PTSD symptom severity, as well as measures of health and functional outcomes will be collected at the beginning and completion of therapy.

3.3 Study Procedures

Retrospective Study. At ENRM VA, we will perform secondary analysis on a database of Veterans who have previously consented and enrolled in the VA Portland Health Care System Sleep Laboratory Data Repository (IRB #3636, "Sleep Disorders Data Repository"). The director

of this data repository, Dr. Miranda Lim, is a co-Investigator on this proposal. Study inclusion/exclusion criteria are as follows: Referral to the VA Portland Sleep Lab for a sleep evaluation; Able to understand the purpose of the data repository and provide verbal and written consent.

The data repository contains sleep polysomnography (PSG) recordings from a multitude of electrophysiological (including EEG) and cardio-respiratory sensors/electrodes that are monitored during the overnight clinical sleep study. Other types of information residing in the database include demographic information, medical history (including diagnosis and treatment history of PTSD, TBI, substance use). All subjects in the data repository have undergone baseline clinical intake evaluation consisting of 7 validated symptom surveys scored that use Likert scales: (1) Epworth Sleepiness Scale (ESS, 8 item): Assesses degree of excessive daytime sleepiness; (2) NIH PROMIS Global Health (NIH-PGH, 9 item): Assesses general physical, emotional, social health, activities of daily living, fatigue; (3) Insomnia Severity Index (ISI, 7 item): Quantifies difficulty in falling asleep, staying asleep, and impact upon daily functioning; (4) Functional Outcomes of Sleep (FOSQ-10, 10 item): Assesses degree of difficulty carrying out certain activities due to sleepiness; (5) Patient Health Questionnaire (PHQ-9, 9 item): Used in screening, diagnosis, monitoring and measuring of severity of depression; (6) PTS symptoms checklist (PCL-5, 20 items: Assesses the 20 items in the DSM-V criteria for PTSD; (7) Rivermead Post-concussive Symptoms Questionnaire.

Polysomnography (PSG). Participants underwent in-lab overnight sleep study, which was followed by performing standard sleep staging by a registered PSG technician and interpreted by a Board-certified sleep physician. The database contains sleep EEG recordings from Veterans with PTSD only (n=107), TBI only (n=126), PTSD and TBI (n=87), depression only (n=80), and controls (no PTSD/TBI/Depression; n=256).

De-identification and Data Transfer to ENRM VA: The PSG recordings in the data repository, comprised of electrophysiological measures (such as EEG, EOG, EMG) will be exported to a binary format and will be completely stripped of any identification marks and will be saved with coded filenames. A separate text file containing epoch by epoch (30 second duration) sleep stages will be also generated for each sleep study with no patient's identification inside the file nor as part of the filename. Other de-identified data includes a spreadsheet with demographic information and survey data from Table 1. The de-identified data will be transferred from Portland VA to ENRM VA via a shared network folder with limited access permission.

Prospective Study I. The retrospective study of the existing database is from clinical sleep studies where 6 EEG electrodes, covering the occipital, central, and frontal lobes of the two hemispheres, were used. This is because all sleep states can be scored by these limited number of electrodes. However, using these 6 EEGs limits the coherence analysis to general areas of the frontal, central, and occipital lobes and with no direct representation for other areas of the brain. The aim of this prospective study is to evaluate potential improvement on the performance of the Neuromarkers using a dense array (up to 64 channels) EEG montage that covers all areas of the scalp. In the control and PTSD subjects, we will perform sleep studies using a dense array EEG montage and will compare the performance of the Neuromarkers in distinguishing PTSD from non-PTSD groups.

This entails starting with the coherence analysis based on the six electrodes used in the preliminary study followed by evaluating the nominal improvement in discrimination ability (PTSD vs. absence of PTSD) with the use of extra channels. The control subjects will be recruited by

advertising in the Bedford VA common areas, and by distributing informational flyers via VA providers, Veteran organizations, and other Veteran networks (including Veteran Services Offices, Veteran Centers, CBOC's, and other programs). We may also place an advertisement on Craigslist. Eligible Veterans will be able to self-refer to be screened for the study. The PTSD group will be recruited from Veterans undergoing treatment of PTSD at ENRM VA before the start of their treatment (Veterans with PTSD recruitment described in Section 4.2.3).

Depending on the outcome of this study and the amount of potential improvements that might be achieved using a denser EEG arrays, we will identify the exact montage to be used in the follow-up prospective study with PTSD patients undergoing psychotherapy. We will thus start with the 6-channel EEG of the standard clinical sleep study, and potentially expand it by including more EEG locations to presumably produce results that are superior (more precise) to those obtained in preliminary studies

Prospective Study II. Up to sixty (60) Veterans with PTSD symptoms undergoing treatment at the ENRM VA will be recruited by the Research Coordinator. The study protocol will be explained to potential subjects which will be given ample time to consider their participation in the study and ask any questions they may have. They may take it home with them if they need more time and then return to the PTSD clinic. If the Veteran agrees to participate, they will sign all informed consent documents and be given a copy to retain. All protocols and informed consents related to this project will be approved by the ENRM VA Institutional Review Board (IRB).

3.4 Data Collection

Sleep Study: EEG data acquisition: Study protocol with respect to overnight sleep study will consist of patients wearing an ambulatory home sleep monitoring device, LiveAmp from BrainProductsCorp. LiveAmp has a small footprint and can record up to 64 unipolar channels where On the days of the sleep studies and supported by the biomedical engineer, the research health specialist of the project will attach the EEG electrodes to the scalp and will demonstrate to the patient as how to attach/detach the EEG electrodes to/from the device as well as how to turn the device on and off when in bed at night, and after waking up in the morning, respectively.

Patients will be instructed on how to wear the cap and attach it to the device while sleeping in their own bed. Furthermore, Over-night live support will be available where the patient will be reminded via phone call to start the study. The patients can also call the technician during the night in case of any difficulty with the continuation of the study. The device will be retrieved the next day after the study when we will examine the quality of the quality of the acquired signals.

These sleep studies will be performed at 4 points of time during their course of the treatment

Study Visit 1. Within one week before initiation of their treatment protocol, to capture sleep EEG data representing pre-treatment phase

Study Visit 2 Within one week after their first therapy session to capture the data and *BCM* that could be used for the development of early predictor of response to treatment.

Study Visit 3 Immediately a at the conclusion of their treatment phase, to capture the data representing recovery from PTSD symptoms.

Study Visit 4 About three months after their last therapy sessions, to capture the data associated with possible remission or relapse.

Screening Questionnaires:

(S-1): Montreal Cognitive Assessment (MoCA) [79]: the MoCA is a brief neuropsychological screening measure that will be used to assess participants' general cognitive status. In order to better account for possible neurodegenerative disorders, we will be using the MoCA to assess cognitive functioning in Veterans older than 65. Veterans who score 26 or higher on the MOCA will be considered eligible to participate in the study.

Demographic, PTSD Questionnaires and Quality of Life Surveys : Data collection protocol will consist of administrating the following:

(D-1): Demographic, Medical History, and Use of Medications forms: Demographic data to be collected will include self-reported age, gender, race, ethnicity, and employment status. Other baseline variables will include time from most recent prior event to screening contact, other traumatic life events and timing, prior history of mental health treatment, and current medications.

(D-2): The Beck Depression Inventory (BDI-II) [**56**]**:** BDI_II 21-item self-report multiple-choice inventory and is composed of items relating to symptoms of depression such as hopelessness and irritability, cognitions such as guilt or feelings of being punished, as well as physical symptoms such as fatigue, weight loss, and lack of interest in sex [67]. The test takes about 10 minutes to complete.

(D-3): Pittsburgh Sleep Quality Index (PSQI) [**57**]: The 15-item PSQI measures quality and patterns of sleep in adults. It takes an estimated 3 to 6 minutes to complete. A global PSQI score greater than 5 has yielded a diagnostic sensitivity of 89.6% and specificity of 86.5% (kappa = 0.75, $p<0.001$) in distinguishing good and poor sleepers. Internal consistency reliability has been estimated to range from .77 to .81.

(D-4): Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF) [**58**] The Q-LES-Q-SF is a self-reported questionnaire that is among the most frequently used outcome measures in psychiatry research (e.g., in clinical trial of PTSD treatment with psycho-therapy methods, [**59**]). The 16-item Q-LES-Q-SF evaluates overall enjoyment and satisfaction with physical health, mood, work, household and leisure activities, social and family relationships, daily functioning, sexual life, and economic status.

(D-5): Patient-Reported Outcomes Measurement Information System® (PROMIS)-29: The publicly available PROMIS instruments contain a fixed number of items from seven PROMIS domains: depression; anxiety; physical function; pain interference; fatigue; sleep disturbance; and ability to participate in social roles and activities. The PROMIS-29, a generic health-related quality of life survey, assesses each of the 7 PROMIS domains with 4 questions. The questions are ranked on a 5-point Likert Scale.

(D-6): PTSD Patient Checklist (PCL-5) [**52**]: PCL-5 is the revised version of PCL-M used in the preliminary studies, where a 20-item self-report assesses the 20 DSM-5 symptoms of PTSD (corresponding to criteria B-E in the above; total symptom severity score ranging from 0 to 80). According to PCL-5 [52], the current estimate for PCL-5 diagnostic cut-point for PTSD is 33 (compared with a value of 50 used for PCL-M of the preliminary studies). Also, similar to PCL-M, it is expected that a change of 10 points in PCL-5 is to be considered as a minimum threshold for clinically meaningful improvement [52].

(D-7): Clinician-Administered PTSD Scale (CAPS-5) [**55**]: CAPS-5 is a 30-item structured interview and is considered the gold standard in PTSD diagnostics and evaluations. It consists of 20 questions to assess the four DSM-5 [**53**] PTSD symptom clusters: Criterion B: Presence of one

(or more) of intrusion symptoms associated with the traumatic event (Items 1-5); Criterion C: Persistent avoidance of stimuli associated with the traumatic event (Items 6-7); Criterion D: Negative alterations in cognitions and mood associated with the traumatic event (Items 8-14); Criterion E: Marked alterations in arousal and reactivity associated with the traumatic event (Items 15-20). CAPS-5 uses a five-point symptom severity rating scale for all symptoms: (0) Absent; (1) Mild/Subthreshold, (2) Moderate/threshold, (3) Severe, and (4) Extreme/incapacitating.

(D-8): Patient Health Questionnaire-9 (PHQ-9) [**70**]: The PHQ-9 is the depression segment of the full PHQ, which scores each of the DSM05 criteria for Major Depressive Disorder (MDD). Items ask about depressive symptoms experienced over the last two weeks and each of the nine items are scored as "0" (not at all), "1" (several days), "2" (more than half the days), or "3" (nearly every day). A total severity score ranges between 0 and 27 points and indicates none to minimal depression (0-4), mild depression (5-9), moderate depression (10-14), moderately severe depression (15-19), and severe depression (20+).

(D-9): Columbia Suicide Severity Rating Scale (CSSRS) [71]: The CSSRS is a state-of-the-art suicide measure that assesses the severity of suicidal ideation for both lifetime and current (i.e., the last 30 days) time frames. Severity of suicidal ideation is rated on a 6-point scale ranging from no suicidal ideation (0) to active suicidal ideation with specific plan and intent (5). Additionally, the measure assesses lifetime and current suicide attempts. The CSSRS demonstrates good internal consistency [72].

(D-10): Brief Addiction Monitor (BAM) [73]: The Brief Addiction Monitor is a 17-item measure of addiction severity.

(D-11): Brief Pornography Screener (BPS): **Brief Addiction Monitor** (BAM) [74]: The BPS is a 5-item measure developed to detect problematic use of pornography among clinical and non-clinical samples. Only those endorsing use will complete the screener.

(D-12): NORC Diagnostic Screen for Gambling Disorders (NODS) **Control, Lying, and Preoccupation** (CLiP) [75]: This is a 3-item diagnostic interview instrument for adult problem gambling and gambling disorder. Only those endorsing use will complete the screener.

(D-13): Adult ADHD Self-Report Scale (ASRS-v1.1) [76, 77]: This is an 18-item self-report measure that evaluates adult ADHD. The ASRS is a highly reliable and valid scale that has also been shown to have high concurrent validity with the rater-administered version. Each item on the checklist is rated either "never", "rarely". "sometimes", "often", or "very often" (76, 77, 78). This screening measure will be used at baseline only.

Table 1 depicts the data collection instruments and the study times**. D1-D13 will be administered on the same days of the EEG sleep studies.**

Data Collection Instrument and Measures		PTSD Subjects			
		Study Visit 1	Study Visit 2	Study Visit 3	Study Visit 4
Demographics	*D-1*	X			
BDI-II	*D-2*	X		X	X
PSQI	*D-3*	X		X	X
Q-LES-Q-SF	D-4	X		X	X
PROMIS-29	*D-5*	X		X	X
PCL-5	*D-6*	X		X	X
CAPS-5	*D-7*	X		X	
PHQ-9	*D-8*	X		X	X
CSSRS	*D-9*	X		X	X
BAM	*D-10*	X		X	
BPS	*D-11*	X			
NODS-CliP	*D-12*	X			
ASRS	*D-13*	X		X	X
EEG Sleep Study		X	X	X	X

3.5 Analysis Plan

Hypothesis 1.1 *PTSD$_{dx}$* will discriminate PTSD patients from control subjects without PTSD; The primary evaluations will be based on computation of *PTSD$_{dx}$* and *PTSD$_{sev}$* markers similar to the approach used in preliminary studies. This will occur in multiple phases, all of which will randomly divide and analyze the full sample of 656 veterans into 3 groups of 219, 219, and 218 subjects, and in proportion to the presenting symptom/condition status of veterans, as follows:

Condition (Group)	Total N	Subsample		
		Sample 1	Sample 2	Sample 3
PTSD only (group **A**)	107	36	36	35
TBI only (group **B**)	126	42	42	42
PTSD & TBI (group **C**)	87	29	29	29
Depression only (group **D**)	80	26	27	27
Controls (no PTSD, TBI, depression) (group **E**)	256	86	85	85

To test our first hypothesis and in the first phase of analysis, we will use the specific *PTSD$_{dx}$* neuromarker previously identified in our preliminary study of 76 veterans, and evaluate it separately in all 3 subsamples. Analysis of covariance (ANCOVA) will be used to compare adjusted mean *PTSD$_{dx}$* scores between the PTSD only group (Group **A**) vs. planned contrasts with the remaining 4 groups. The a-priori-defined contrasts will consist of the following 5 comparisons: **A** vs. **E**, **A** vs. **B/C/D** combined, **A** vs. **B**, **A** vs. **C**, and **A** vs. **D**. Thus, for each subsample, there will be 5 planned comparisons, and hence a total of 15 comparisons. We expect the largest differences in mean *PTSD$_{dx}$* scores between PTSD only (group **A**) and controls (Group **E**), but nonetheless, also expect the PTSD only group to have higher mean *PTSD$_{dx}$* scores than Groups **B**, **C**, and **D**.

In these analyses, models will be adjusted for potential confounding variables (e.g. current use of sleep medications) identified by use of student *t*-tests (or Wilcoxon tests) for continuous variables and chi-square tests for categorical variables. Given the 5 planned comparisons for each subsample, a modified p-value of 0.01 will be used to define statistical significance. While arbitrary, "validation" of the previously identified *PTSD$_{dx}$* neuromarker will be based on statistical significance as follows: (i) all 3 comparisons of Group **A** vs. Group **B** at $p<0.01$, AND at least 9 of the 12 remaining comparisons at $p<0.01$.

In the second phase of this hypothesis, the approach used to identify the most promising *PTSD$_{dx}$* neuromarker described in Preliminary Studies will be applied to the much larger dataset of 656 veterans. For this analysis, Subsamples 1 and 2 will serve as training (development) samples, and Subsample 3 will serve as the validation sample. For subsample 1, ANCOVA will again be used to identify the 5 most promising *PTSD$_{dx}$* neuromarkers (based on corresponding *F* and *p*-values) rank ordered across the 5 planned comparisons described above. This process will be repeated for Subsample 2. From these results, the most promising *PTSD$_{dx}$* neuromarker will be selected based on the lowest aggregate rank scores across both subsamples and across all 5 planned comparisons. Once this this *PTSD$_{dx}$* neuromarker is identified, it will be formally tested using the 5 defined planned comparisons within Subsample 3, and again using a *p*-value of <0.01 to define statistical significance. In aggregate, these analyses will determine whether the originally identified *PTSD$_{dx}$* neuromarker can discriminate between veterans with and without PTSD, and whether a potentially

more promising $PTSD_{dx}$ neuromarker is identified.

Hypothesis 1.2: $PTSD_{sev}$ will strongly correlate with PTSD symptom severity level

Using the same database as in retrospective study and focusing only on PTSD subjects, an analogous approach to that described for hypothesis 1.1 will be used. The principal difference will be that the independent variable, $PTSD_{sev}$, is a continuous variable rather than a categorical variable. Therefore, multiple linear regression will be used with $PTSD_{sev}$ as the independent variable, and the PCL-5 symptom severity scale as the dependent variable acquired on the day of the sleep study. We will also examine the correlation of $PTSD_{sev}$ with the other measures of quality of health and life in the database, particularly RQP (Rivermead Post-Concussive Symptom Questionnaire), PHQ-9 (Patient Health Questionnaire), FOSQ (Functional Outcome of Sleep Quality), ISI (Insomnia Severity Index), and Promis-29. The results of these analyses will provide a comprehensive examination of this hypothesis with respect to how accurately $PTSD_{sev}$ can determine the severity of PTSD, and how well it is correlated with quality of life measures.

Hypothesis 2: Use of a dense array (up to 64 channel) EEG montage, as compared to 6-channel EEG, will improve discrimination of PTSD patients from control subjects without PTSD.

For this analysis, the most promising $PTSD_{dx}$ neuromarker identified in Hypothesis 1.1 (phase 2 development and validation analysis) will be prospectively evaluated in up to 25 PTSD and control subjects. First, a standardized effect size (mean difference / standard deviation) and corresponding 95% confidence interval will be calculated for the $PTSD_{dx}$ neuromarker using the conventional 6- channel EEG approach. Then, using forward stepwise linear regression, extra EEG electrodes whose addition increases the model coefficient of determination (R^2) by at least 1% will be included as candidate extra EEG channels. Once a final model is fit (with >6 electrodes), the corresponding standardized effect size and 95% confidence interval will be calculated. Given the pilot nature and sample size for this analysis (n=25), interpretation will not be based on formal statistical testing, but rather on the difference in the two effects sizes generated from the 6-channel EEG analysis vs. the >6-channel EEG analysis. Given that effect sizes can be interpreted as “small” (0.2), “medium” (0.5), or “large” ($\geq$0.8), we will use half of the width of adjacent categories (i.e. 0.15) to interpret meaningful improvement with the use of more than 6 EEG channels. For example, if the standardized effect size for the 6-channel EEG was 0.70, the >6-

channel EEG effect size would need to be $\geq$0.85 to indicate meaningful improvement and potential indication for a more complex EEG testing approach.

Hypothesis 3: $PTSD_{sev}$ will strongly correlate with the changes of PTSD symptoms and other measures of Quality of Health and Life as a result of psychotherapy.

For this analysis, change in $PTSD_{sev}$ identified from Aim 1 is the primary independent variable of interest and change in CAPS-5, PCL-5, BDI-II, Q-LES-Q-SF, and PSQI serve as dependent variables. Since the CAPS-5 will be administered at only 2 time-intervals, multiple linear regression analysis will be used adjusting for baseline CAPS-5 score and CAPS-5 score after treatment as the dependent variable. For the PCL-5, BDI-II, Q-LES-Q-SF, and PSQI there will be 4 outcome measurements corresponding to pre-treatment, within one week after the initiation of therapy, at the completion of treatment, and at three-months post therapy. For these measures, linear mixed models will be used to examine the strength of association between the slope (change) for $PTSD_{sev}$ and the slope for the dependent variables (evaluated in separate models). To assess if the rate of change is curvilinear, a quadratic parameter will be tested. Due to multiple

observations per subject, an autoregressive correlation structure will be specified to account for within-subject correlation. Also, given 5 outcome variables of interest, a "corrected" p-value of <0.01 will be used to define statistical significance.

4.0 Human Subjects

4.1 General Characteristics

The project has three groups of human subjects' involvement:

1. A retrospective study, where the analyses will be applied to a large existing database of health-related and functional outcome measures, as well as sleep EEG recordings. Database contains sleep EEG recordings from Veterans with PTSD only (n=107), with TBI only (n=126), with both PTSD and TBI (n=87), with depression only (n=80), and controls (no PTSD/TBI/Depression; n=256. The inclusion of records from TBI and depression only groups is to provide training data for the neuromarker to become maximally sensitive and specific to PTSD in the presence of co-morbidities such as depression and TBI.
2. Prospective study 1 with up tp 25 PTSD and control PTSD (n=10) and control (n=10) where we will evaluate potential improvement on the performance of the neuromarkers using a dense array (up to 64 channel) EEG montage. For each participant, we will perform 2 sets of sleep studies that will be at least one week apart.
3. Prospective study 2 in a cohort (n=60) of Veterans undergoing psychotherapy, where we will evaluate the sensitivity of neuromarkers to the improvements in PTSD symptoms, and other functional and HRQoL measures, in response to psychotherapy. These participants will undergo sleep studies at four times of time (a) Within one week before initiation of their treatment protocol; (b) Within one week after their first therapy session; (c) at the conclusion of their treatment phase; and (d) About three months after their last therapy sessions

4.2 Inclusion of Vulnerable Subjects

Vulnerable subjects will be enrolled in this study. These subjects are part of VA population and will not be specifically recruited.

4.3 Inclusion of Pregnant Women

Pregnant women will not be included in this study

4.3 Inclusion of Incompetent Subjects

We will not enroll incompetent subjects in this study

4.4 Inclusion/Exclusion Criteria

Inclusion Criteria. Veterans who meet diagnostic criteria for PTSD. Prior traumatic experience(s) does not have to be direct combat (e.g. may include search and rescue of combat operations). Persons previously treated for PTSD will be eligible so long as current diagnostic criteria are present. Specific inclusion criteria are as follows:

1. Adults aged 18 and older: In order to better account for possible neurodegenerative disorders, we will be using the MoCA to assess cognitive functioning in Veterans older than 65. Veterans who score a 26 or higher on the MoCA will be considered eligible to participate in the study.

2. Current (past 3 months) diagnosis of PTSD as indicated by medical record review.
3. Ability to read and speak English to complete surveys and participate in therapy.
4. Explicit denial of suicidal or homicidal ideation or intent, which will be corroborated by reviewing the patient chart

Exclusion Criteria:

1. Brain injury prohibiting speech, writing, and purposeful actions.
2. Identified to have current suicidal or homicidal ideation (immediate referral to a crisis center/hospital).
3. Major confounding psychiatric disorder; i.e. assessment indicates presence of:

    (i) Major mental health disorder that involves psychosis; or

    (ii) Otherwise in the state of psychological crisis (appropriate referral to occur).
4. Current or recent (within 1 month of study entry) DSM-5 substance use disorder.
5. Individuals who are taking either illicit or prescribed Rx that could interfere with EEG, including benzodiazepines and certain mood stabilizers. This will be done by (a) asking what medications they are taking and (b) checking their medical records while screening for possible participants.

4.5 Recruitment Procedures

To reach the larger population of Veterans, one recruitment strategy will consist of the distribution of informational flyers via VA providers, Veteran organizations, and other Veteran networks. Research study staff will also give recruitment presentations to primary care providers, mental health clinicians, and other providers at the Bedford VA to enhance recruitment. This will only take place with the proper approvals from local VA- and non-VA programs that support Veterans (including Veteran Services Offices, Veteran Centers, CBOC's, and other programs). Additionally, at Crossroads events in the ENRM VA Hospital, too, information (e.g., flyers) about the present study and other investigators' studies will be distributed at a table in a highly frequented area of the hospital. Eligible Veterans will be able to self-refer to be screened for the study.

In addition, the recruitment process will include the following:
The names of Veterans coming to the following clinics at ENRM VA for appointments: Tobacco Cessation Program, Veterans Community Care Center (VCCC), Mental Health Clinic (MHC), the Community Stabilization Program (CSP), Primary Care Behavioral Health (PCBH), the Community Residential Center (CRC), and the VASH program.

These names will be obtained by searching CPRS for entry/provider codes associated with these programs. Research Study Staff will access these Veterans' medical records only to determine whether they meet the study eligibility criteria for psychiatric diagnosis/ suicidal intent.

We will then send a letter to the Veteran to invite him/her to learn more about the study (attached to this application) and will also include the recruitment flyer (will be presented to the IRB committee before the start of recruitment of the first subject). The letter will contain contact information for the research team, so the veteran can contact the research team for more information. It will state that if we don't hear from the Veteran within two weeks, that we will call

and contact them about the study. It will also state that if Veterans do not want to be called, they can call our research staff and let us know. The identifiable information will be used only by members of the research team. This information will not be disclosed to anyone outside the VA.

4.5.1 Subject Identification and Pre-Enrollment Screening:

Callers will first be provided information about the study purpose and procedures and given time to ask all questions they may have. If the Veteran is interested in the study, a screening will take place using a brief screening assessment. Eligible participants will be scheduled to meet with the PI or study staff, who will obtain informed consent from the interested participants.

4.5.1a Use of PHI for Recruitment and/or Screening before consent is obtained:

Our protocol will request a waiver of HIPAA authorization for recruitment and screening purposes.

4.5.1 b Consent for Recruitment and/or Screening:

Our protocol will request a waiver for informed consent for recruitment and screening purposes.

4.5.2 Enrollment:

At initial assessment (Study Visit 1) research study staff will discuss the study and consent with the potential participant and allow the subject unlimited time to decide to participate. Confidential spaces will be acquired for an initial in-person interview and consenting procedure, to be conducted at the Bedford VA.

4.5.2a HIPAA Authorization:

Potential subjects will sign a freestanding authorization form.

4.5.2b Informed Consent:

Participants will sign a consent form. Research Coordinator. The study protocol will be explained to potential subjects which will be given ample time to consider their participation in the study and ask any questions they may have. They may take it home with them if they need more time and then return to the PTSD clinic. If the Veteran agrees to participate, they will sign all informed consent documents and be given a copy to retain. All protocols and informed consents related to this project will be approved by the ENRM VA Institutional Review Board (IRB).

4.5.2c Master List

The subject's name will be added to the master list immediately after consent. Master list will be maintained in a double lock procedure: locked in a cabinet located within a locked office.

4.5.2d

VHA health record will not be created

4.5.2e Certificate of Confidentiality

A certificate of confidentiality is not needed for this research.

4.6 Risk/Benefit Ratio

4.6.1 Potential Risks and Methods to be Used to Minimize Risks:

Potential Risks: PTSD is a disabling anxiety disorder with high rates of comorbid disabling symptoms including sleep disturbance, depressive disorders, panic disorder, substance misuse or dependence, high somatic symptom severity, decreased role functioning, and an increased risk of suicidal behavior. Left untreated, PTSD can persist for decades if not over an entire life span. Thus, any therapy that can be delivered safety and effectively in the treatment of PTSD offers substantial potential benefit to the affected individual.

Participation in the study carries the risk of unanticipated breach of confidentiality. With regards to EEG sleep studies, the proposed method of acquiring Neuromarkers in the PTSD subjects involve LiveAmp hardware from Brain Products GmbH, Germany during an overnight home sleep study. Such devices are battery-operated and routinely used at the sleep laboratories and patient's home for the clinical/research assessment of sleep and neurological disorders. Potential risk could possibly be minor skin irritation associated with wearing the electrode cap the attachment/detachment of EEG electrodes which will be minimized by following routine clinical sleep study procedures.

Risk of COVID-19 exposure: Coming into the hospital/lab for a research EEG test may increase the risk of COVID-19 exposure. The exposure risk would be the same with clinical EEG appointments and we are taking the necessary precautions to minimize this risk (see below).

Protection Against Risks

(1) Retrospective studies, confidentiality is protected by storage of all study PSG records and questionnaires behind a VA firewall and accessed by permission and password. The PSG recordings in the data repository, comprised of electrophysiological measures (such as EEG, EOG, EMG) will be exported to a binary format and will be completely stripped of any identification marks and will be saved with coded filenames. These de-identified PSG records will thus be converted to a series of numbered binary files containing a matrix of the raw data (EEG/EOG/EMG in microvolts) with no patient identification associated with the file. A separate text file containing epoch by epoch (30 second duration) sleep stages will be also generated for each sleep study with no patient's identification inside the file nor as part of the filename. Other de-identified data includes a spreadsheet with demographic information, survey data from Table 1, and information about PTSD therapy. The de-identified data will be transferred from Portland VA to ENRM VA via a shared network folder between the two VAs and limited access permission.

(2) Prospective Studies: Risk, confidentiality, and data security will be minimized via use of good clinical practices including recording, storage, transfer, and analysis on de-identified data files extracted from sleep records and D1-D6 surveys, locking all data files, use of a subject identification code system, maintenance of data only on a secure system, and recording data without HIPPA identifiers. Subjects will be able to terminate the testing at their request at any time without prejudice. Study information will be entered into the password protected database accessible via secured-internet connection. The database sits behind VA firewall on a secure VA server and will utilize whole database encryption technology. Only registered users

will be assigned a password to access the database for online data entry or data transfer. When study personnel leave the study, their access to the study materials and database will be terminated. Instruments D1-D13 will be recorded on laminated paper data collection forms with a permanent marker and responses will be directly entered into the REDCap site for the project. Laminated forms will be erased and sanitized with an alcohol wipe after data has been entered. Informed consent forms will be kept in locked file cabinets at ENRM VA.

(3) Protection against risk of COVID-19: Lab staff will be tested for COVID-19 on a bi-weekly basis and will be in full appropriate PPE (including mask, face shield or goggles, gown, and gloves) during all in-person interactions. Before arriving on campus, participants will be given updated hospital policies, the link to the hospital screening questions, and a map with the most direct route to the lab. Upon arrival in the lab, Veterans will be given a surgical mask and hand sanitizer. Lab staff will ask the Veteran the screening questions again and take their temperature to ensure safety before entering the lab for the research assessment. The lab space and all surfaces and equipment will be thoroughly cleaned and sanitized before and after each visit. This plan was developed following the guidelines of labs currently conducting clinical EEG assessments at VA hospitals.

4.6.2 Data and Safety Management Plan:

The sleep studies protocol of this project coincides with the duration of PTSD treatment which can last as long as 12 sessions over several weeks/months. Subjects would therefore be monitored by the clinicians before and after the patients undergo their home sleep study (as part of their routine therapy). Patients will be advised to contact the PTSD clinic-clinical coordinator immediately in the event of any unforeseen difficulties with wearing the device during sleep including excessive interference with their comfort. In case of such occurrence, patients will be advised to detach the electrodes from their scalp and face, and wash the site of electrode attachment with soap and warm water.

The database sits behind VA firewall on a secure VA server and will utilize whole database encryption technology. Only registered users will be assigned a password to access the database for online data entry or data transfer. When study personnel leave the study, their access to the study materials and database will be terminated. Instruments D1-D13 will be recorded on laminated paper data collection forms with a permanent marker and responses will be directly entered into the REDCap site for the project. Laminated forms will be erased and sanitized with an alcohol wipe after data has been entered. Informed consent forms will be kept in locked file cabinets at the ENRM VA Hospital.
To ensure data quality and minimize missing data, several levels of data checks will be implemented. First, when data collectors enter data into the data entry program, they will be notified which fields have been skipped. In general, all fields with the exception of some text fields will have valid codes associated with them, so that no true blank variables should exist in the database. Furthermore, when appropriate, skip patterns will exist for some variables, which can automatically populate variables that would then be considered "not applicable". Second, the data entry program will also not allow an entry that isn't considered valid mostly through the use of drop down controls in which only valid answers are presented.
All efforts will be made to minimize missing data from these key variables. Any reasons for missing data will be recorded for each patient for a global sensitivity analyses to examine the effect of missing-ness on the conclusions of the study hypotheses. Also, the linear mixed effects modeling approach described for aim 3 can accommodate missing outcome data with

confirmation that they missing data appear to be missing at random. Moreover, multiple imputation will be used to fill in missing values.

Data will be kept in keeping with VA regulations, which are 7 years post-closing of the study. Data access will be limited to study personnel. If a study team member were to be removed from the protocol, access to the data would likewise be terminated. In the unlikely event of data being lost, the IRB will be informed immediately.

4.6.2.2 Data Safety Monitoring

Retrospective Studies. Confidentiality is protected by storage of all study PSG records and questionnaires behind a VA firewall and accessed by permission and password.

De-identification and Data Transfer to ENRM VA. The PSG recordings in the data repository, comprised of electrophysiological measures (such as EEG, EOG, EMG) will be exported to a binary format and will be completely stripped of any identification marks and will be saved with coded filenames. These de-identified PSG records will thus be converted to a series of numbered binary files containing a matrix of the raw data (EEG/EOG/EMG in microvolts) with no patient identification associated with the file. A separate text file containing epoch by epoch (30 second duration) sleep stages will be also generated for each sleep study with no patient's identification inside the file nor as part of the filename. Other de-identified data includes a spreadsheet with demographic information, survey data from Table 1, and information about PTSD therapy. The de-identified data will be transferred from Portland VA to ENRM VA via a shared network folder between the two VAs and limited access permission.

Prospective Studies.

Risk, confidentiality, and data security will be minimized via use of good clinical practices including recording, storage, transfer, and analysis on de-identified data files extracted from sleep records and D1-D13 surveys, locking all data files, use of a subject identification code system, maintenance of data only on a secure system, and recording data without HIPPA identifiers. Subjects will be able to terminate the testing at their request at any time without prejudice.

Study information will be entered into the password protected database accessible via secured-internet connection. The database sits behind VA firewall on a secure VA server and will utilize whole database encryption technology. Only registered users will be assigned a password to access the database for online data entry or data transfer. When study personnel leave the study, their access to the study materials and database will be terminated. Instruments D1-D13 will be recorded on laminated paper data collection forms with a permanent marker and responses will be directly entered into the REDCap site for the project. All data will be entered before COB on the collection date and laminated forms will be erased and sanitized with an alcohol wipe after data has been entered.). Informed consent forms will be kept in locked file cabinets at ENRM VA.

4.6.3 Potential Benefits

It is unlikely that participation in this study will benefit participants. It is hoped that data collected in this study will enable development of objective means of assessing PTSD that will

greatly enhance PTSD diagnosis and management. Diagnosis for PTSD is currently established on the basis of a patient's clinical history, mental status examination, duration of symptoms, and clinician administered symptom checklists or patient self-reports. The novel PTSD biomarker developed in this study could contribute to a more precise and objective diagnosis of PTSD and its severity level, selection of specific evidence-based treatments, objective evaluation of treatment efficacy, and also for predicting who might be at the risk of relapse.

4.7 Costs and Payments

Participants in the study will receive either a voucher or a gift card for the amount of $100.00 for each test day, which amounts to a total of $400.00 for their participation in Tests 1-4. If they withdraw from the study, they will be compensated for all of the study parts that they have completed by the time of their withdrawal.

4.8 Providing for Reuse of Data

Participants will be given the option to have their data be added to the "EEG" data Repository, a new data repository being set up here at the ENRM VA Hospital, for future research studies pertaining to EEG data collection and approved to be data banked. All data will be stored and maintained according to VA regulations and only investigators approved through the EEG data repository committee will have access to this data. Any future use of the data will be reviewed and approved by this committee. The creation and management of this data repository will be approved by the hospital IRB and Research and Development committee before any data from this study will be stored in it for future use. Once the Data Repository has been approved, an amendment to this project will be submitted to store the data in the data repository.

5.0 Resources

- Research Lab
- Equipment and personnel time will be covered by the grant

6.0 Collaborations

All of the retrospective and prospective studies will be performed at Bedford ENRM VA. Outside collaborators include Dr. Miranda Lim at Portland VA, and Dr Kevin Kip at Tampa VA. Dr. Lim is the director of a Portland VA project for developing a data repository that contains EEG sleep records and clinical outcome measures from Veterans with PTSD, TBI, and depression. She will supervise the efforts of the research assistant at Portland VA with regards to transferring the data from this data repository to Dr. Modarres for utilization in the development of algorithms and predictors for human PTSD subjects.

Dr. Kip is a Biostatistician and will provide guidance to the PI for the statistical analysis of the data, which will be all performed by the PI Dr. Kip will not have access to the data.

7.0 Qualifications of the Investigators

Dr. Modarres is a biomedical engineer/scientist with experience and expertise in brain monitoring and novel analysis techniques and clinical assessment of this technology. His R&D effort in the past 25 years has centered around developing state-of-the art monitoring devices and analytical methods that have been applied to quantify sleep and brain function abnormalities and disorders. His experience includes having been the Principal Investigator on a number of multi-year NHLBI, NIMH, NINDS, DOD, and VA supported grants on the development and clinical

testing of novel, neuro-physiologically based techniques for objective assessment of brain function. He is also the first author on a manuscript that describes the preliminary findings, and sole inventor on A VA sponsored patent application, on the novel neuro-physiological based markers of PTSD to be further validated in the current VA merit grant supported by this IRB.

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