Protocol Title: Neurofeedback Impact on Chronic Headache, Sleep, and Attention Disorders Experienced by Veterans with mild Traumatic Brain Injury

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BACKGROUND AND SIGNIFICANCE

Veterans, while serving in Iraq and Afghanistan, may have had exposure to improvised explosive devices (IEDs). These blast exposures resulted in the "signature injury" (Haywood, 2008) of these operations, traumatic brain injuries (TBIs). The over-pressurization shock waves emitted from the blast causes human brain injury, which may be considered a mixed mechanism injury event; involving both a focal (direct impact of brain's surface on the bony protuberances of the skull) and diffuse injury (stretching and twisting of axons and blood vessels by shearing forces) (Chapman & Diaz-Arrastia, 2014). The blast event injury is generally followed by a secondary, longer duration injury related to the activation of molecular and biochemical responses stemming from the initial blast injury. This secondary injury was once thought of as self-limiting (hours or days post-injury); however recent findings suggest that the abnormal brain signaling and inflammatory processes last much longer and can lead to long term symptoms (Chapman & Diaz-Arrastia, 2014). In addition, these processes can cause a disruption of normal brain connectivity (Hayes, Bigler, & Verfaellie, 2016), abnormal electrical brain waves and patterns, as well as disruptions of intra- and interhemispheric communication, which can persist from acute to chronic stages in many patients (Taber, Warden, & Hurley, 2006). The changes in the brain stemming from TBI may persist and even progress in the long run. Recent evidence has confirmed the long-suspected association between TBI and the development of neurodegenerative diseases later in life (McKee, 2014). The majority of blast related injuries are not detectable by current neuroimaging strategies, e.g. computed tomography (CT) or magnetic resonance imaging (MRI) (Datta et al, 2009) but rely on self-report of blast exposure and its effects for TBI diagnosis (Davenport, 2016).

The prevalence rate of TBI for Service Members (SMs) involved in these operations is estimated to be 20% (Swanson et al, 2017; Chapman & Diaz-Arrastia, 2014) with about 80% of these injuries considered mild(m)TBI (Chapman & Diaz-Arrastia, 2014). It has been suggested that the actual rate of mTBI may be under-reported (up to 50%) (Kontos et al, 2013) since cognitive disturbances associated with TBI may impact SM's memory of the blast experience (Chapman & Diaz-Arrastia, 2014) and SMs who are caught up in the battle may not report blast exposures (Okie, 2005). The residual effects of mTBI can also be unrecognized, undocumented, under reported, misinterpreted or misdiagnosed as only psychological (Kontos et al, 2013). Most SMs, who experienced mTBI, appear to recover within hours or days, however for a significant number, estimated at 23-48%, symptoms persist (Chapman & Diaz-Arrastia, 2014; Dean, O'Neill, & Sterr, 2012) and may persist for many years post injury (Lange et al, 2013).

SMs and Veterans with mTBI can fatigue easily and have disordered sleep, headache, dizziness, irritability or aggression on little or no provocation, as well as experience anxiety, depression, or affective lability and changes in personality and cognitive functioning (Kontos et al, 2013; Duff, 2004). When these symptoms persist, they can negatively impact Veterans' self-rated health (McGregor, Dougherty, Tang, & Galarneau, 2013), occupational status (ability to return to work, school) social functioning (relationships, participation in groups) (Morissette et al, 2011) and quality of life (Reddy, Rajeswaran, Bhagavatula, & Kandavel, 2014). The etiology of some of the persistent post concussive symptoms (PCSs) that are often attributed to mTBI have been challenged by some researchers as being due to posttraumatic stress disorder (PTSD) and depression rather than mTBI (Kontos et al, 2013; Hoge et al, 2008). Research has been conducted over the last several years to determine which PCS's are strongly associated with mTBI. Among those PCSs found were headaches (Hoge et al, 2008; Theeler & Erickson, 2012; Dean, O'Neill & Sterr, 2012; Couch & Stewart, 2016); problems with sleep (Ayalon et al, 2007; Grima et al, 2016) cognitive dysfunction, specifically taking longer to think (Dean, O'Neill, & Sterr, 2012), concentration issues (attention) (Cooper et al, 2010), impaired working memory, (Dean & Sterr, 2013) and slowed reaction time (Kontos, 2013). Others have found that the cognitive impairments seen with mTBI are more strongly related to the co-existence of PTSD (Shandera-Ochsner et al, 2013) than with mTBI alone. However, given that the estimate of PTSD co-occurrence with mTBI is suggested to be upwards of 60%, (Chapman & Diaz-Arrastia, 2014) the exact mechanism would seem to be less important than the actual experience of cognitive dysfunction and its impact on a Veteran's life.

Researchers have also purported distinct relationships of PCSs and their impact on each other and other issues, such as: that headaches and memory PCSs may be the actual mechanisms accounting for the relationship between TBI and PTSD and depression (Morissette et al, 2011); that patients with mTBI sleep complaints are more likely to suffer with headaches, depression and irritability symptoms (Chaput et al, 2009); and that sleep issues associated with wartime mTBI are the etiology of cognitive dysfunction specifically in sustained attention and memory (Collen et al, 2012). Regardless of the exact relationships, it clear that these PCSs have profound effect on Veterans' physical and mental health as well as their quality of life. Of note, the comorbidity of sleep disturbance associated with mTBI and PTSD was considered a significant challenge to VA health providers when caring for these patients because of its persistent nature and limited treatment options (Sayer et al, 2009).

Developing and implementing strategies to reduce the persistent symptoms associated with mTBI is of critical importance. Veterans diagnosed with mTBI and experiencing PCSs present growing treatment challenges to the healthcare system due to limited or suboptimal treatment options (Hoge et al, 2008; Institute of Medicine, 2011; Koski et al, 2014). Currently, treatment for PCSs is symptom-focused. For instance, Veterans with migraine headaches associated with mTBIs are often treated with abortive agents (i.e. Triptans) and preventive medications (i.e. anticonvulsants and tricyclics) (Theeler & Erickson, 2012). Cognitive dysfunction and insomnia are treated with cognitive rehabilitation programs, cognitive behavior therapy (CBT), occupational therapy, and medications (i.e., hypnotics for insomnia) (Ayalon et al, 2007). Symptom management is just that, applying a temporary fix on symptoms or addressing concerns one at a time. While cognitive rehabilitation and psychological support are widely used to treat mTBI PCSs, neither has been shown to be effective in addressing the core brain deficits associated with mTBIs (Duff, 2004). Since symptoms often return and persist, it is clear that improved treatment options for these persistent PCSs need to be developed for Veterans with mTBIs (Morissette et al, 2011).

Rather than a symptom management approach, Defina and colleagues (2009) describe the possibilities of brain repair in TBI by treatments that would enhance neuroplasticity. Although the concept of neuroplasticity was first presented in the 1940's and further developed in the 1990's, it is only recently that neuroplasticity training and interventions have been developed (Defina et al, 2009). According to Defina and colleagues, neuroplasticity interventions may establish a more normalized or stable brain environment and enable the brain to re-organize itself and function more normally. The use of specific neurotransmitters or hormones that are related to the biochemical cascade of TBI, as well as, electromagnetic stimulation, nutraceuticals, median nerve stimulation and neurofeedback have been suggested as possible treatments to effectively normalize the brain environment and maximize natural healing. The benefits of neuro enhancement strategies could potentially reduce suffering and improve quality of life (Clark & Parasuraman, 2014).

Neurofeedback (NFB) is a sub-specialization of biofeedback (Larsen and Sherlin, 2013; Hammond, 2011). Biofeedback is defined as a method of treatment that trains patients to become aware of and learn to control their own physiology to improve physical and psychological health (Thomas, 2012). The NFB system is able to reflect a person's (referred to as the trainee) brain wave pattern instantaneously back to the trainee through conventional electroencephalography (EEG) providing salient information to which the trainee can respond accordingly.

NFB has been demonstrated to influence cortical neuroplasticity significantly (Enriquez-Geppart, Huster, & Herrmann, 2013; Ros, 2013) and can lead to actual and meaningful microstructural changes in white and gray matter (Ghaziri et al, 2013). NFB has been shown to contribute to neuronal rehabilitation by changing connectivities of specific areas of the brain that may have been impaired and these rehabilitative changes appear to be permanent (Ibric, Dragomirescu & Judspeth, 2009). Functional (f)MRI studies further validate that NFB may be useful in promoting recovery from neurological disorders that are linked to abnormal patterns of brain connectivity (Haller et al, 2013; Koush et al, 2013). Hence, this non-invasive and non-pharmacological method may be used to 'normalize' abnormal network activity by manipulating and thereby strengthening region specific brain networks (Haller et al, 2013).

PRELIMINARY STUDIES AND CURRENT STATUS OF THE FIELD

In 2018-2019, the principal investigator conducted a pilot project to assess the feasibility of conducting a full clinical trial as required by a granting agency. To meet the granting agency's requirements for resubmission, this pilot had to be completed in a one-year period. In addition to a determining its feasibility, this pilot study's objective was to evaluate NFB training as a low risk, non-invasive, effective treatment for Veterans who had sustained an mTBI, also referred to as concussion, while serving in the military. The chronic PCSs targeted were headache, insomnia, and attention difficulties. Perceived quality of life was also assessed pre and post intervention. It was hypothesized, that those Veterans who received NFB training would experience a clinically significant: 1) reduction in the frequency and/or severity of headaches; 2) decreased severity of insomnia and/or enhanced perceptions of sleep; 3) improved attention; 4) improved perceptions of quality of life; and 5) the study is feasible to conduct at VA Pacific Islands Health Care System (VAPIHCS).

This Institution Review Board (IRB) approved the pilot study which used utilized a prospective design to carry out all the procedures that would be involved in conducting a full clinical trial.

Regarding feasibility, the pilot project revealed that nineteen Veterans were very interested in participating in the pilot study, however, due to the parking situation at the facility (often takes 30 minutes to 1.5 hour to find parking), 5 said it would be too difficult and 4 others said because of travel time and gas costs they simply could not afford to come. Interestingly, 6 others did not want to be in the control group since they indicated it would not benefit them in any way. Two of these Veterans asked if they could receive treatment afterward or if they could be guaranteed treatment in the funded study. About 3-4 others had interest, but had current travel plans or intense school schedules. Table 1 Outlines the Strategies that will be used in this clinical trial to address the issues with feasibility.

Table 1 Participation Issues and Strategies to Address

Issue with Participating	How Addressed in Clinical Trial
Gas/travel time costs	Participants will receive $20.00 for gas and time
Parking is very difficult	Participants will receive valet parking ($7.00)
Control group benefit	1. Will receive intervention at the end of control group participation 2. Will receive graduated remuneration for assessments taken at baseline (25.00), 4-6 weeks ($50.00), 8-10 weeks ($50.00) and a 2-month follow-up ($100.00) 3. 15-minute weekly calls from an investigator on health topics for 8 weeks
Schedule of participation	Study will run over a 5-year period, participants can join at a time that is convenient to their schedule (when not traveling or have a less intense school schedule)
Work schedule	Extended and weekend hours will be added as needed.

In a one-year time frame, internal funding was found to purchase the NFB equipment, the PI received training on the new, updated equipment, IRB approval was obtained, and the study was conducted. Time constraints of the Grant re-submission deadline limited the possible number of participants to those that could be recruited and complete NFB intervention in a 3-month period. The PI was able to recruit 4 Veterans with a deployment related mTBI and PCSs including headaches, insomnia, and attention difficulties into the study. These participants were available and willing to participate despite the possibility of being randomized into the control group and the travel time, parking and gas costs. All 4 received the intervention.

The four participants demonstrated significant clinical gains from pre-intervention to post-intervention in each of the clinical areas assessed: headache (HIT & NeuroQOLTBI headache), sleep (ISI & NeuroQOLTBI sleep), attention, and quality of life (NeuroQOLTBI Satisfaction & Ability and QOLATBI), as well as on scales that measured PTSD (PCL-5), Depression (PHQ9), Anxiety (DASS21) and general symptoms (GSI) (for a fuller description of these instruments, please refer to the clinical trial instruments that are listed in a later table). See Table 2 for a summary of the Pilot data.

Table 2	Summary of Pilot Outcome Data				
Questionnaire	**Mean value at Entry (S.D.)**	**Mean value at Follow-up (S.D.)**	**Mean change from Entry to Follow-up (S.D.)**	**Hypothesis would be Supported**	**Clinically Significant Change**
HIT	63.75 (6.60)	43.50 (8.39)	**20.25**	YES	2.3 points
NEUROQOLTBI Headache	59.93 (4.43) (T-Score)	50.38 (7.93) (T-Score)	**9.55**	YES	7 points
NEUROQOLTBI Sleep	66.48 (4.94) (T-Score)	48.23 (2.50) (T-Score)	**18.25**	YES	7 points
ISI	22.75 (2.50)	3.25 (1.50)	**19.50**	YES	3 points
QIK	13.00 (17.53)	0.75 (0.96)	**12.25**	YES	30%
NEUROQOLTBI Satisfaction	38.63 (13.03) (T-Score)	50.45 (9.98) (T-Score)	**-11.82**	YES	7 points
NEUROQOLTBI Ability	40.48 (13.20) (T-Score)	52.35 (9.03) (T-Score)	**-11.87**	YES	7 points
QOLATBI	50.38 (12.63)	88.43 (10.89)	**-38.04**	YES	30%
PCL	54.00 (14.63)	10.75 (9.00)	**43.25**	YES	10 points
PHQ9	15.00 (2.00)	2.25 (2.22)	**12.75**	YES	5 points
DASS21	61.00 (11.85)	15.00 (5.32)	**46.00**	YES	12.7 points
GSI	69.50 (7.94)	38.00 (22.91)	**31.50**	YES	Less

The subjects did not communicate any adverse reactions. While enrolled in the study, comments of some of the participants included, “I finally can think more clearly. I haven’t been able to do that for years”; “my headaches are gone, I never believed that could ever happen”; “I am falling asleep at night, just like that, I don’t have to have a few drinks to fall asleep any more”; “I have not had to use any headache medications” [during the course of NFB treatment]; I have not had to use any Adderall at all” [during the course of NFB treatment].

Since all of the procedures that would be needed in a full clinical trial were able to be conducted, the pilot study determined that conducting a full clinical trial was feasible. The data obtained from the four Veterans were very positive. Findings supported each of the hypotheses and participants demonstrated significant clinical gains on the 12 different questionnaires used to assess the outcome of the intervention.

In addition, the Principal Investigator (PI) of this current project had previously collected comprehensive outcome data in private practice. Among 432 clients seen over a five-year period, only a small percent of clients, less than 5% (n=19) did not complete their course of treatment of 10-40 sessions. The number of sessions depended on an agreed amount from the outset of care. Three clients moved (1 continued NFB with another provider), 1 mother with 3 children returned to work and felt she could not continue, but hoped to return, and 15 did not give the PI of this project a reason for leaving, although 2 had indicated finances were an issue.

All clients were asked to identify their top 5 symptoms that they wanted to address, and invariably sleep issues was one of their choices. At the start of each session, the client was asked to rate their experience on the 5 symptoms on a 1-5 scale. Without exception, it was found that sleep was the first symptom positively impacted.

Post treatment, there was a large percent (94%) of clients meeting or exceeding their outcome goals, which were established prior to treatment, and 6% who did not entirely meet their goals but indicated satisfaction with

what was achieved. Clients came in for NFB for a variety of reasons, stress/anxiety [n= 103], attention issues (both adult and children) [n= 88), pain syndromes [n= 32], headache (migraine, tension, and mixed type) [n= 60], depression [n= 23], sleep [n= 25], and other [n=99] (i.e., irritable bowel syndrome, attachment disorder, etc. as well as those who wanted peak performance training). With the success with NFB in the civilian population, the PI of this project wants to bring NFB to VAPIHCS Veterans to provide an effective non-pharmacological solution to address very significant and often debilitating health issues.

The use of NFB is not new to the military. Studies as early as 1971, were published on the use of NFB for enhancement of sleep in military officers under stressful conditions (Sittenfeld, Budzynski, & Stoyva, 1976) and in 1984 on the use of NFB in enhancing peak performance of SMs under stressful conditions (Budzynski & Stoyva, 1984). Although both studies were successful, with the war ending and resulting in reduction of funds for the Department of Defense (DoD), continuing efforts in these areas were abandoned at that time. The 1990's brought renewed interest in the use of NFB with Vietnam Veterans (n=14) who were hospitalized with PTSD. All of the Veterans undergoing NFB treatment experienced a resolution of their nightmares and flashbacks. Only one Veteran remained on medication at the conclusion of the study but the medication dosage was reduced by half (Peniston & Kulkosky 1991). The Peniston PTSD NFB protocol used in the study was very specific leading to varying degrees of study replicability, most likely due to inadequate training of the researchers providing the NFB treatments. With the advent of new psychotropic medications and other therapies at that time, interest in NFB by the military decreased in the latter 1990's. More recently, with the high cost, limited efficacy and potential for adverse effects of medications, coupled with enhanced NFB technology and a growing body of research supporting its efficacy, there is a renewed interest in NFB.

NFB has been used since the 1960's for symptoms related to mTBI. Duff (2004) in his extensive review of the literature, suggests that since the 1960's, studies using NFB, (EEG biofeedback or neurotherapy) have shown that patients can be taught to promote normal functioning in brains with excessively slow wave activity, which is often found in post-concussion syndrome. In a 2013 review of the literature, May and colleagues used a 10-level classification rubric (10 being the highest level e.g. randomized control trials; to the lowest 1 being case study/anecdotal evidence) to classify the research literature of NFB and mTBI. They found two studies at level 5 (randomized waitlist or intention to treat), six studies at level 3 (historical control), ten studies at level 2 (no control group) and five studies at level 1 (case study/anecdotal evidence). Of the 23 studies reviewed, all found NFB to positively impact symptoms associated with mTBI (attention, memory, quality of life, sleep, motor control, coordination, depression, headaches). May and colleagues called for more randomized control group studies and suggested the need for double blind and sham NFB studies (2013). Recent studies have continued to demonstrate support for the use of NFB with symptoms related to mTBI. Nelson and Esty (2012) found in their small study (n=7) that neurotherapy significantly reduced depression, somatic and memory/attention symptoms, when employed with Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) Veterans diagnosed with TBI and PTSD. A study conducted in 2013 demonstrated that NFB was able to enhance quality of life and perceived control in 29 SMs with mTBI and PTSD (Strang & Chae, 2013). In a control group/waitlist study conducted in 2014, sixty mTBI participants (aged 18-49 years old) received NFB, and it was found that 20 sessions of NFB significantly improved quality of life (Reddy, Rajeswaran, Bhagavatula, & Kandavel, 2014). Munivenkatappa and colleagues in 2014 provided further validation of the ability of NFB to enhance structural and functional connectivity and cognitive scores of mTBI patients. Arns and Kenemans in 2014 reported in their review of the literature regarding attentional and sleep disorders that NFB is associated with improved sleep quality and sleep onset.

After a thorough meta-analyses of NFB research, Larsen and Sherlin rated NFB "probably" efficacious for the treatment of mTBI symptoms (2013), with its limitation being the lack of randomized controlled trials with a large enough sample to obtain power. NFB has been demonstrated as effective in treating symptoms related to mTBI in a sizable number of case reports and research studies. It would appear that the next logical step would be to conduct a randomized control clinical trial evaluating NFB in treating specific persistent PCSs. As post-traumatic headaches, attention problems, and sleep issues were identified as common PCSs (Rigg & Mooney, 2011), this proposed study will therefore target those Veterans with deployment associated mTBIs and who are experiencing those PCSs of chronic headaches, insomnia and attentional difficulties. Since persistent PCS symptoms have been demonstrated to impact quality of life, this variable will also be evaluated (Reddy, Rajeswaran, Bhagavatula, & Kandavel, 2014). Quality of life is considered one of the most clinically important variables since it a central part of patients' everyday functioning and experience (Frisch, 2004).

There are currently 86 (23 complete and 63 active) NFB studies listed on ClinicalTrials.gov. The clinical trials are focused on NFB's impact on: Attention Deficit Disorder (19); PTSD (6); depression/anxiety/emotions (14); addiction both alcohol and food (6); pain to include back, neuropathic, spinal cord injury (14); TBI (3); motor rehabilitation (5); autism spectrum (3); and other disorders such as Multiple Sclerosis, tinnitus, Tourette's, Parkinson's, Stroke and Premenstrual Syndrome (16). There is one clinical trial relating to a specific NFB Technology referred to as Global Z NFB for persistent post-concussive symptoms in SMs. However, this latter study focuses on active duty SMs and their emotional issues relating to TBI. No currently listed study on Clinical Trials.gov is focused on Veterans with mTBI PCS of chronic headache, insomnia and attention disorders.

The purpose of this research project is to evaluate the impact of NFB on chronic post-traumatic headaches, insomnia, attention disorders, and quality of life in Veterans diagnosed with mTBI.

Although double blind, sham studies have been suggested with NFB, the PI of this study and others (Sitaram et al, 2017; Schabus et al, 2014) believe sham (in the case of NFB, providing feedback based on false feedback, random or another person's brain waves to participants in a control group) controls may cause unintended and untoward outcomes and therefore would be unethical. Given the nature of the NFB processes (participants receiving and intentionally impacting their brain wave activity that is instantaneously being fed back to them), providing "sham" feedback may cause disinterest at best and anxiety, frustration and possible rage at worst in participants. The PI of this study was previously involved in a double-blind study in which she and study participants were able to determine after only 5 to 10 minutes if the neurofeedback was real or sham, therefore removing any potential for benefit from conducting a blind study. In addition, the sham feedback led to one study participant's disengagement (looking at wall and ceiling), another's physical and mental discomfort, and another's frustration to such an extent that he literally ripped off the electrodes and refused to continue. After the adverse events experienced by the participants in the control group, the PI of this study withdrew from participation for ethical reasons as the benefit did not appear to outweigh the additional risk. Therefore, the proposed study design for this research is a randomized controlled study.

OBJECTIVES/AIMS/HYPOTHESES

The objective of this randomized control clinical trial is to provide data on the clinical impact of neurofeedback (NFB) treatment OEF-OIF-Operation New Dawn (OND) Veterans diagnosed with mTBI and experiencing persistent post-concussive symptoms as compared to a randomized control group, who will only receive usual care. Comparisons will be made at baseline, at the study treatment midpoint (around 4-6 weeks), and conclusion of study treatment (around 8-10 weeks) and at a two-month follow-up. The effect of NFB will be assessed on the following:

1. Frequency of headaches as measured by NEUROQOLTBI headache tool, and headache impact on functioning as measured by Headache Impact Tool (HIT-6)

2. Severity of sleep disturbance as measured by Insomnia Severity Index (ISI) and quality of sleep as measured by the NEUROQOLTBI Sleep disturbance tool.

3. Attentional functioning as measured by computerized visual attention performance test (QIKTest) accuracy index

4. Quality of life as measured by Quality of Life after Brain Injury (QOLABI) and NEUROQOLTBI Satisfaction with roles and activities & Ability to Participate in roles and activities.

5. General physical and emotional symptoms possibly co-occurring with mTBI as measured by self-report using General Symptom Scale (GSI), Depression, Anxiety and Stress Scale (DASS21), Post-Traumatic Stress Disorder Checklist (PCL), Patient Health Questionnaire-Depression (PHQ9), and NEUROQOLTB Positive affect and wellbeing short form.

We aim to conduct a full-scale trial to determine whether NFB is a clinically relevant intervention in the care OEF-OIF-OND Veterans with mTBI who are experiencing chronic symptoms of headaches, insomnia and attention difficulties.

Hypotheses

We hypothesize that the intervention group, receiving NFB training over the course of treatment, relative to the control group, will experience a clinically and statistically significant change in scores that indicates:

1. decreased severity of headaches on the NEUROQOLTBI headache tool and enhanced functioning on the HIT-6.

2. greater improvement in perceptions of quality of sleep on the NEUROQOLTBI Sleep disturbance tool and decreased severity of sleep disturbance on the ISI.

3. greater improvement in attention function in the QIKTEST accuracy index.

4. greater improvement in quality of life as shown by enhanced involvement in roles on the NEUROQOLTBI Satisfaction with roles and activities & Ability to Participate in roles and activities tools and on the QOLATBI baseline scores.

5. greater improvement in general physical and emotional symptoms score on the PCL-5; on the PHQ9; on the DASS21; on the GSI, and on the NEUROQOLTBI Positive affect and wellbeing tool

RESEARCH DESIGN AND METHODS

The proposed study is a randomized controlled clinical trial using NFB, also known as EEG biofeedback, as the study intervention. The control group members will continue with their usual care and will receive a 15-minute phone call from an Investigator on a weekly basis to briefly discuss one of eight possible health topics that the treatment group would receive as a normal part of their NFB session, with the only difference is the treatment group will receive NFB. The NFB special use system will read and interpret a participant's brain wave pattern which will be instantaneously fed back to the participant providing information, to which a participant can respond accordingly. The NFB specialist assumes a coaching role with people training on the NFB special use system to assist in the achievement of a focused relaxed state, which enhances the overall brain functioning. The significance and unique aspect of NFB is the direct impact on physiological dysregulation, which is the basis of this treatment approach. As mentioned previously, interventional theories have indicated that NFB may promote the neuroplasticity of the brain (Defina et al, 2009; Ibric, Dragomirescu & Judspeth, 2009) and thus enhance brain healing (Defina et al). Through the use of biofeedback mechanisms, participants can mediate their own brainwave patterns. Therefore, the scope of the impact of NFB may include all functions under the active management by the central nervous system. NFB also enhances perceptions of health self-efficacy by providing direct and continuous feedback, which fosters the participants experience of self-regulating specific brain aspects (Carlson-Catalano & Ferreira, 2001), which can lead to brain healing (Enriquez-Geppart, Huster, & Herrmann, 2013). Assisting Veterans to self-regulate brain wave activity through NFB technology has the potential for significant positive changes in their health and well-being, as well as their perceptions of self-health management and overall quality of life.

The specific NFB special use system that will be used is the Cygnet Neurofeedback System from Bee Medic Corporation. The PI in her private practice has had the opportunity to use four different NFB systems. The Cygnet NFB System was by far the most efficacious in its ability to positively engage the person in his or her own training, the most specific in eliciting response to the person's brain wave patterns and had the best overall effect on outcomes. The latest technological advances in this special use system has enabled training frequencies in the infra-low frequency range as well as in all other relevant frequency ranges which is a breakthrough capacity not available on any other NFB system. This will enable the individualized training to the person's brain training preference. Neither the PI nor members of her family or friends has any part in the ownership in this company, nor is there an existence of a conflict of interest for the PI in selection of a NFB system for this project. The NFB equipment will be independent of the VA IT network. The Cygnet NFB special use system to be used during the course of this study is comprised of a desktop computer or laptop, that is a special use system that is not connected to the VA network, with dual monitors fully loaded with operational Cygnet NFB system with Neuroamp and Alpha-theta feedback capability. The special use system will have the following Cygnet NFB software packages: Dreamscapes; Dual Drive Extreme; Train Adventures; Inner Tube; Particle World; Roller Ball; Hyper Pong; and Tropical Heat. Each of these software packages offer a method for the trainee to engage in training based on participant preference. Some of the packages offer adventure strategies, (i.e., trains moving forward or planes flying to navigate different areas such as tunnels or mountains), outdoor enjoyment (flower opening; butterflies flying), or even a personalized experience (a movie of choice) all for the purpose of moving forward the point of interest (plane, train, flower, butterfly or movie)

when trainees' brainwaves are in a calm focused state. All of the software packages are equal in capability to inform trainees of their physiological brain wave patterning and responses.

Twenty, one-hour, NFB training sessions will be provided to each participant in the intervention group by a trained NFB specialist over an 8-10-week period. Participants in the intervention group will receive up to 5-sessions but usually 3 sessions a week. Participants in the control group will continue with their usual treatment and will receive a 15-minute call for eight weeks from an Investigator on a health topic. This will help to keep members of the control group engaged in the project and receive the same information that is offered to the intervention group members. The health topics that are generally discussed during NFB sessions include sleep hygiene, basic nutritional concepts, beverage choices, positive thinking, thought reframing, fitness, daily calming activity, and enhancement of focus strategies. When a control group member completes his or her final assessment, he or she will be offered the NFB intervention over an 8-10-week period and will become part of the post-control intervention group.

Similar to other types of physiological training, it takes repeated exposure for the physiological learning, in this case demonstrated by the brainwaves to consolidate. According to published literature, 15 to 30 sessions (mean of 20 sessions), have been used in NFB training related to headaches; (Moshkani Farahani et al, 2014; Naderi & Jorjorzadeh, 2015; Nelson & Esty, 2015) usually 2-3 times weekly. Having at least twice weekly sessions provides the consistency of the training to promote the necessary physiological learning. In the PI's private practice, 20 sessions twice weekly was the most efficacious in achieving the physiological learning level desired. With the newest technology equipment used in this study, that enables a more specific and individualized focused treatment, it has been found that more frequent sessions are tolerated well and preferred by its recipients. Once started, people receiving NFB feel better in general and usually complete the entire 20 sessions.

The feedback provided will be multi-modal. The visual feedback feeds back various aspects of EEG-derived information, and this is complemented with an audio signal stream that similarly reflects the relevant aspects of the EEG. Finally, a tactile feedback capability is provided so that the feedback is experienced as immersive. Each of the signals corroborates and reinforces the others for a more compelling training experience.

Neurofeedback Treatment Sessions: NFB treatments of study participants will be provided by one of three or four VA licensed employees who have received NFB formal training (referred to as NFB specialist). The PI will be one of the three or four NFB Specialists. Two or three of the NFB specialist will receive formal and ongoing training and will be supervised by the PI who has extensive experience in NFB and is Board Certified by the Biofeedback Certification and International Alliance (BCIA) Board. A coaching script will be developed and used by the NFB specialists during the NFB training sessions to keep the coaching approach consistent.

The treatments will be conducted in areas designated by the VAPIHCS Space Committee and the areas will comply with human research standards (e.g., privacy, safety). All procedures will be explained in advance to participants and voluntary participation affirmed. An abbreviated general symptom checklist comprised of the symptoms most important to the participant will be evaluated on a scale of 1-10 each session by the participant as to his or her current status and results of the evaluation will be used to direct each training session. Participants will be trained using specific defined protocols for treatment. Although specific mTBI protocols will be outlined, the actual equipment settings used will be individualized to the participant's symptoms and response (Niv, 2013; Hammond, 2011), as consistent with the patient-centered care philosophy of the VA. The NFB specialist will carefully document all settings used and responses to treatment. Session training forms, which record all settings, electrode placements and the results obtained, will be used at each session to assure treatment consistency and determination of participant goal attainment.

Study participants will be seated in a comfortable chair throughout the treatment session. Common EEG electrodes with a pre-application of EEG adhesion conductive paste will be placed on the participant's scalp. Scalp placement will be pre-determined by the participant's main presenting symptoms and be placed per the 10-20 International System of Electrode Placement (Hughes, 1994). Sites that will be most frequently used are Right Back (T4-P4), Right-Left (T3-T4), Right Front (T4-Fp2), Left Front (T3-Fp1), and Left Back (T3-P3). After adequate electrode contact quality is determined through direct measurement of contact impedance and offset voltage, the participant will receive instruction and coaching as they look at the game training screen and attempt to focus on the moving image (an airplane, a flower that opens and closes, etc). The game training screen will provide almost instantaneous feedback (within 200 milliseconds) (Huster et al, 2014) to participants

about brain functioning as they participate in the attainment of certain goals. For instance, a participant's goal may be to move forward (i.e. airplane) or open up (i.e. flower) the image. Participants may be asked to take slow breaths and clear their minds as they gently focus on the image on the screen. As the participant progresses in achieving the goal, the neuronal networks are enhanced. It is the heightened effectiveness of the communications across neuronal pathways that begin to resolve abnormal brain patterns.

Each person's brain has a particular setting on the neurofeedback equipment it prefers, and it may take a few sessions before the NFB specialist identifies that particular setting. When that setting is identified certain symptoms, for example, insomnia, may get better. Until the NFB specialist finds that particular setting, although unlikely, it may be possible that some symptoms may feel a little worse. This is not bad thing since it informs the NFB specialist more about a person's brain and the particular setting that a brain prefers can be found more quickly. The NFB specialist can always find that preferred setting especially with the individual's help by letting the NFB specialist know how they are feeling. If worsening of symptoms occurs, it is very short-term, and is not usually more than a minor discomfort, and can be easily adjusted.

As with any training, multiple sessions (in this case 20) are needed to reinforce the optimal patterns (Hammond, 2011; Reddy, Rajeswaran, Bhagavatula, & Kandavel, 2014).

Neurofeedback is not currently the standard of practice in the mTBI clinic at the VA Pacific Islands Health Care System (VAPIHCS). All participants in both the NFB treatment group and control group will continue to receive their usual care related to their mTBI wherever they may be receiving it. An example of usual care/standard of practice at VAPIHCS includes: Once OEF-OIF-OND Veterans receive a positive screen for mTBI, (i.e. screening questions suggestive of a possible concussion or mild TBI while deployed in OEF-OIF-OND), the Veteran is evaluated with a the Level II TBI evaluation (comprehensive TBI evaluation). At this visit, an in-depth history of the actual event(s) is obtained and the VA/DoD (2016) criteria are used to determine if a Veteran experienced a concussion/mTBI as well as the nature and severity of post concussive symptoms including headaches, attention and concentration impairment, and insomnia. These standardized assessments are performed by a small number of trained providers at the VAPIHCS and results are documented in the VA's electronic medical record. Once a diagnosis is established, the treatment and rehabilitation is symptom-driven (e.g. if the Veteran suffers from migraine-like post-traumatic headaches, are treated according to standard of practice for migraine headaches). Any other symptoms significantly impacting the Veteran's quality of life are treated accordingly as well (e.g. low back, neck, foot, shoulder pain, concentration difficulties, and /or insomnia). Any psychological issues such as depression, anxiety, or PTSD are treated according the standard of practice for psychiatry/psychology per VA/DoD Clinical Practice Guidelines. In summary, in regard to treatment, VAPIHCS follows the mTBI guidelines for symptomatic treatment published by the VA/DoD (2016).

Veterans may also enter the VA with an existing post-9/11 deployment-related mTBI/concussion diagnosis from the DoD If this occurs, Once enrolled into the VA, DoD diagnosed Veterans would receive a Follow Up Consultation to assist with treatment and rehabilitation planning.

Veterans with a post-9/11 deployment-related mTBI/concussion diagnosis which had been given by a community provider may also be eligible to enter the study.

Definition of study variables: In Veterans that experienced a blast-related mTBI injury during deployment

mTBI: A blast-related brain injury based on patient self-report or witness accounts that include loss or alteration of consciousness and posttraumatic amnesia with possible transient neurological deficits (Chapman & Diaz-Arrastia, 2014)]
Insomnia: is frequent difficulty with falling or staying asleep or early morning awakenings resulting in daytime impairments (Wallace et al, 2011).
Posttraumatic Chronic Headache: is persistent head pain, usually migraine however can be tension type or mixed that is chronic (at least 6 months) in nature and experienced at least 2 times a week and impacts daily functioning (Theeler & Erickson, 2012).
Attention dysfunction: is difficulty with attention that impacts daily functioning (Cooper et al, 2010).
Quality of life: is an individual's perception of life satisfaction and ability to carry out various daily life functions (Truelle et al, 2010).

Pre-intervention data on these variables will provide the baseline assessment of where participants are at the outset of treatment. Since the post-traumatic headaches, sleep and attention issues in the participants have

persisted over time, it is assumed that changes in these variables will be in large part attributable to the treatment and not chance. Having a control group of similar patients will provide objective evidence of the intervention's efficacy. In addition, the subjects randomized to neurofeedback will also receive "usual care". Therefore, whatever advances in care occur during the course of the study should affect treatment and control group usual care groups equally. Any medication or treatment changes will be captured on a tracking form of medication and treatments at each of the four assessment sessions.

It is projected that the Veteran participants receiving NFB therapy (in addition to their usual care) will show greater improvements in insomnia, headaches and attention and report higher gains in quality of life as compared to Veteran participants receiving only usual care for mTBI related persistent symptoms.

Accessible Population and Methods of Recruitment.

Leadership of VAPIHCS, the Neurology Clinic and TBI cognitive rehab have expressed complete support of the full proposal submission. VAPIHCS has 533 active OEF-OIF-OND mTBI patients who live on Oahu have completed a comprehensive Level II assessment (see Table 3). Active patients are those: with a current zip code in the VAPIHCS catchment area, without a date of death, that are NOT a fictitious test patient for documentation training purposes (name begins with "ZZ"), and that have had a visit anywhere in VAPIHCS within the last 2 years. The following Table indicates the number of active patients for all of VAPIHCS and the number of OEF-OIF-OND active patients diagnosed with mTBI who completed a Level II TBI evaluation living on Oahu. These data were pulled on February 11, 2019.

Table 3. Number of Patients and Active OEF-OIF-OND mTBI Patients who completed a Level II TBI Evaluation at VA PIHCS

Category	Veterans
All active Patients	33,407
All OEF/OIF/OND	2,554
OEF/OIF/OND with mTBI	1,530
OEF/OIF/OND with mTBI Living in Oahu	956
OEF/OIF/OND with mTBI Living in Oahu with Level II Evaluation	533

In addition, the mTBI clinic at the VAPIHCS has been enrolling about 10 new mTBI patients per month for the last 6 months. This may be due to the new Veteran access policies implemented. With the increasing clinic enrollment, it is anticipated that by the time funding is received, the study obtains IRB approval, and recruitment begins in early 2020, the numbers on Oahu would increase to about 600 OEF-OIF-OND Veterans with mTBI and who have completed a Level II TBI evaluation.

Seventy-two participants (36 in each group, intervention and control) are needed to complete this study. To achieve this number, 100 participants may be recruited, or 17% of active OEF-OIF-OND mTBI patients who completed a Level II TBI evaluation. Although, Veterans diagnosed with mTBI who participate in this study must also be experiencing headache, insomnia and attention disorders, these symptoms are commonly experienced by the OEF-OIF-OND Veterans cared for at VAPIHCS. OEF-OIF-OND Veterans are young motivated individuals who are actively seeking novel effective methods to address their symptoms. Up to 100 Veterans may be recruited since it is estimated that up to 28% may dropout, to achieve the 72 enrolled participants to complete the study.

If needed, the study investigators will widen announcement and recruitment to Hawaii community OIF-OEF-OND Veterans not enrolled in the VAPIHCS. According to the American factfinder, for the year 2017, American Community Survey (1-year estimates), there are 30,989 Veterans (9/2001 and later) living in Hawaii. The Rand Report (Baiocchi, 2012) indicates that approximately 65% of Service Members deploy, which would mean that there are an estimated 20,142 Veterans (9/2001 and later) who were deployed and now are living in Hawaii. According to experts, approximately 20% of post 9/2001 deployed Veterans experienced a mTBI (Swanson et al, 2017), which would mean that there are about 4,028 Veterans living in Hawaii who experienced a mTBI. Interested community recruited Veterans without a formal mTBI diagnosis will be screened and enrolled into the VAPIHCS TBI program and will be given a Level II evaluation, if necessary, and those meeting the inclusion criteria will be enrolled.

The proposed sample size is sufficient to determine statistical significance. Recruiting 36 participants with mTBI per treatment arm (total 72) from the projected estimated 600 VAPIHCS active OEF-OIF-OND patients (with a Level II mTBI evaluation) and 4,028 estimated community residing Veterans with mTBI (if needed) is feasible. Several neurologists who work within the VA and the community who are currently treating Veterans with mTBI have agreed to support recruitment as well.

Recruitment at VAPIHCS: A waiver of Health Insurance Portability and Accountability Act (HIPAA) approval will be applied for to access VAPIHCS names, phone numbers and addresses of active OEF-OIF-OND patients with mTBI diagnoses for recruitment purposes. IRB approved letters will be sent to each actively enrolled OEF-OIF-OND Veteran with the diagnoses of mTBI. If we have not heard from the Veteran by two weeks after the letter was sent, we will call him or her by phone to check on letter receipt and answer any questions. After three phone attempts, with no answer, we will remove the name. The letter will explain the planned study and will provide contact information should the Veteran desire more information. It is conservatively estimated that 40 letters will need to be mailed out and 40 phone calls made each week in order to fulfill recruitment goals. Adjustments to this schedule will be made as needed to complete recruitment on time. In addition, new mTBI patients will be directly recruited from the mTBI clinic by the providers who perform initial evaluations. Names, phone numbers and addresses used for recruitment purposes will be destroyed at the completion of the recruitment process. Also, IRB approved flyers and letters will be distributed to Veterans enrolled in the mTBI Clinic. The mTBI clinic staff, when possible, will inform patients of the study and provide contact information. In addition, staff will provide names of patients to the study staff they deem to fit the eligibility criteria when possible.

Recruitment in the Community: Presentations will be made to clinicians and providers who specialize in neurology, in addition to clinicians and providers who regularly work with the Veteran community. The IRB approved letters and flyers will be provided to them. The clinicians and providers will be asked to distribute flyers with study contact information. OEF-OIF-OND Veterans from the community will need to provide verification from their provider of their mTBI diagnoses. Community recruited OEF-OIF-OND Veterans without a diagnosis will be screened and enrolled into the VAPIHCS TBI program and given a Level II TBI evaluation.

Letters and Flyers will be developed for distribution that indicate the study title, purpose, participant requirements, inclusion and exclusion criteria, risks and benefits and contact number if interested in hearing more about the study. No coercive statements or undue inducements will be included in these materials. All recruitment materials will be submitted to the IRB for approval. IRB Approved Announcements of the study will be made to IRB approved forums to reach as many Veterans as possible:

- Veteran Council Group meetings (monthly/quarterly) flyer distribution and presentation
- Social Media (i.e.VAPIHCS and/or VA National Facebook)
- Oahu Veterans Center (Facebook and webpage)
- VA Volunteer Service stakeholder quarterly meeting – usually 25+ different agency representatives attend who are providing services to Veterans from the community.
- Newspaper article on study
- Press release at no-cost
- VA and Pacific Health Research and Education Institute (PHREI) media list and contacts
- Publicized at monthly outreach events which target Veterans
- UH and other University Student Veterans Association
- National Guard Office bulletin board
- State Office of Veterans Services (Statewide Vets Flash e-list and website as well)
- My HealtheVet National Webpage- State site specific information
- Announcements at mTBI group meetings or sessions
- Tripler Army Medical Center's e-newsletter TAMC 360
- An IRB approved advertisement will be placed in local military and civilian newspapers (involves cost)
- IRB approved flyers will be placed in supermarkets and community centers
- Electronic Bulletin Board at Tripler Army Medical Center's entrance will announce study and provide contact numbers

Procedures to Monitor Enrollment

An Excel spreadsheet will be developed to track enrollment by each Quarter. A dashboard with the projected enrollment numbers and the current enrollment numbers will be developed and reported at each weekly meeting. At each weekly meeting strategies will be discussed, and a plan devised to meet enrollment goals.

Procedures to Track/Retain Participants for Follow-up assessments

Participants in the control and intervention groups will be fully informed about the 2-month follow-up assessment during the information session and the consenting process. The importance and significance of the follow-up assessment will be included in all discussions about it. An efficient tracking system will be developed to be able to locate the participant. Patients will be asked to verify their address and phone numbers and an alternate phone number. Participants will be asked the best time of day they would prefer to be notified about their follow-up assessments. Procedures will include: an appointment card will be given to the intervention and control group participants, for those in the intervention group, a thank you card for his or her completion of the neurofeedback training will be sent to the participants home and for those in the control a thank you card for participating in the control group will be sent to the participants home one-month prior to the assessment with time and date of the follow-up assessment and both the control and intervention group participants will be called a week, a day before, and the day of the follow-up assessment. We have provided for a $100.00 payment (gift card) for completion of the follow-up assessment, in addition parking and gas will be covered. Staff will be trained to provide for a welcoming environment and use motivational interviewing techniques and address any concerns regarding returning for the follow-up assessment. If the participant is unavailable for an in-person visit, questionnaires may be mailed and returned to the study team. The decision for a mailed assessment will be decided by the study team on a case-by-case basis.

To create connection and interaction with the control group participants, one of the investigators will hold 15-minute weekly telephone conversations for 8 weeks on health focused topics related to sleep, attention, headaches that would normally be discussed at NFB intervention sessions as appropriate. The topics would relate to nutrition, sleep hygiene, fitness, and positive thinking strategies. This process will also serve to retain the control members in the study and enhance participation in the assessment sessions.

Inclusion/Exclusion Criteria

Inclusion Criteria:
a. OEF-OIF-OND Veterans diagnosed with mTBI
b. Male and non-pregnant females
c. Between ages of 18 and 65, inclusive
d. Complaints of chronic headaches, insomnia, and attention difficulties
e. Able to read and write English
f. Able to comprehend what they read
g. Able to follow directions

Exclusion Criteria:
a. Pregnant female Veteran
b. Non OEF-OIF-OND Veteran who is diagnosed with mTBI
c. Under the age of 18 or over the age of 65
d. Severe TBI
e. Impaired decision-making capacity
f. Unable to comply with study visit schedule
g. Suicide Intent as indicated by a positive response to questions 3, 4, 5, or 8 on the Columbia Suicide Severity Rating Scale (C-SSRS) secondary screen

Justification for Exclusion Criteria: To reduce any possible risk to pregnant women and the possible hormonal influence on headaches experienced and sleep patterns (Karli et al, 2012), pregnant women (or women who are planning to become pregnant in the next eight months) will be excluded from participating in this study. Research findings have demonstrated that sleep issues increase and migraines diminish during pregnancy (Karli et al, 2012), which would impact the results of this study. Veterans under the age of 18, and over the age of 65 will not be included in this study since the legal age for enlisting into the United States (US), military is 18 and Veterans over the age of 65 since those who are older would probably not have served in OEF-OIF-OND. Restricting population to OEF-OIF-OND Veterans allows for a more homogenous sample (e.g.

similar mode of injury) for comparison purposes. In addition, there would be less likelihood of long-term chronic illnesses (e.g., heart disease, diabetes, and or cognitive decline) to make comparisons less viable. Participants must be able comprehend consent and decide to participate in study or not. A Teachback process (ask participant to summarize a paragraph just discussed and write out one sentence) will be used to ascertain the ability to comprehend consent form and ability to read, write and follow directions. Since the Veterans with mTBI are experiencing chronic PCS may be at risk for suicide, they will be screened for suicide intent during the consenting session using the C-SSRS Secondary Screen. If a positive screen is obtained, the consenting process will be stopped. The following will occur depending on Veteran preference/need: Veteran will be walked over to the Ambulatory Care Clinic Mental Health front desk for triage (or if in PTSD Recovery Program give a warm hand-off to the psychologist on duty); the 24-hour crisis hotline called (1-800-273-8255 or 988); or 911 called if there is imminent danger.

Screening Procedures: Using a prepared script for consistency, potential participants will be screened for eligibility at the initial contact. See above inclusion and exclusion criteria. The potential participants will be asked if they have a diagnosis mTBI stemming from military experiences and currently experiencing chronic headaches, insomnia and attention issues; are either a male or female OEF-OIF-OND Veterans between the ages 18 to 65, in addition, females will be asked if they are pregnant or intend to be in the next 8 months; are able to read and write English; are able to comprehend what they read; and are able to follow directions. In addition, they will be asked if they are able to comply with study visit schedule. The Veteran will be questioned to ensure understanding of the purpose of the study. Female Veterans will be informed that if they become pregnant during the intervention phase of study they will be removed from active engagement with an intervention but will be followed through the course of the study and will complete the assessments.

Challenges and Alternative Strategies: Obtaining the required number of participants and retaining participants are concerns for most studies. In February 2019 there were 533 OEF-OIF-OND Veterans with mTBI confirmed by a level 2 evaluation at PIHCS and a potential of over 80 more will be enrolled by December 2019 (the projected timeframe of recruitment for this study to begin) enrolling up to 100 to meet the sample size of 72 Veterans (or about12% of the projected population) is highly feasible. Inclusion of Veterans who receive their mTBI diagnosis from the DoD or from community providers will increase the pool of eligible participants. These are young, otherwise physically healthy and motivated Veterans who are seeking novel approaches to address their health issues. We are confident that we will be able to recruit 72 for participation over the course of the recruitment period. It is conservatively estimated that 40 letters will need to be mailed out and 40 phone calls made each week in order to fulfill recruitment goals. Adjustments to this schedule will be made as needed to complete recruitment on time. In addition, new mTBI patients will be directly recruited from the mTBI clinic by the providers who perform initial evaluations. However, in the unlikely event that the enrollment numbers are not met, it may become necessary to extend recruitment to the community to obtain the sample size. In addition, completion of 20 sessions of NFB and all 4 assessments may be a challenge to the study's success. This clinical study involves active participation of the Veteran volunteers over a 3-4½ month period. In order to determine the efficacy of NFB, the required number of participants must complete the entire trial and assessment sessions. Attrition rates for NFB have been between 10- 30% as demonstrated in a previous NFB studies. Conservatively we are planning up to a 28% attrition rate. In order to enhance retention over the course of the study, this study will compensate participants for their parking, gas and time ($27.00 gift card). All subjects will receive payment for the pre, mid, post and follow-up assessment sessions, for a total of $225.00 in gift cards per subject. The remuneration for the assessments, in the form of gift cards, will be given in a graduated manner to enhance completion rates to include the 2-month follow-up assessment session. Each of the four assessment sessions will take approximately 2.5 hours of time and each subject will receive a $25 gift card for the baseline assessment, a $50 gift card at midpoint of treatment and completion of treatment and a $100 gift card for the 2-month follow-up assessment session. In addition, subjects in the intervention group will receive a $27 gift card, for gas, time, and parking each time they complete an NFB and assessment session. Each subject in the intervention group will complete 20, one hour, sessions over an 8-10-week period; receiving two-three sessions weekly. Subjects in the post control intervention group, will receive compensation of a $27 gift card for gas, time and parking for the 20 NFB and assessment session and a $50 gift card at midpoint of treatment and completion of treatment and a $100 gift card for the 2-month follow-up assessment session. The gift cards (electronic claim codes) will be housed in a password-protected research project file on the R-drive within the VA server, and carefully tracked by the research coordinator. Gift cards will be distributed in person or alternative method (e.g., US Postal Service, electronic communication). If distributed in person, each participant will indicate that he or she received the gift card on a tracking spreadsheet and it will be

cosigned by a research team member for verification purposes. If the gift card(s) is mailed, staff will send the gift card(s) using a return receipt method (e.g., certified mail) to ensure delivery to the participant. A letter will be included with the mailing. The letter will list the visit date(s) and type (e.g., assessment, treatment) associated with the gift card(s). Staff will maintain contact with the participant (e.g., phone call advising of mailing date) to help ensure successful delivery. The return receipt will be filed with the participant's study chart. If the gift card(s) is delivered electronically, the message will include a table with a list of the visit date(s) and type (e.g., assessment, treatment) associated with the gift card(s).The message will ask the participant to reply to the message to acknowledge receipt of the gift card(s). The message will be saved and filed with the participant's study chart.

In addition, interventions will be offered at hours and days that would enable Veterans who work to participate. Phone calls will be made as session reminders, the week and day before as well as on the day of appointment. In addition, a paper monthly calendar with the appointments indicated that can be hung on the wall will be given as well as an appointment card at the end of each session. In addition, those in the control group, will be offered NFB training, after they complete the control group requirements.

Outcome Measures: Outcome measures will be used to compare the results of the NFB intervention and control group. Statistical tests and analyses will be conducted to determine the existence of statistical differences between the intervention and control group measures and on the measures at pre-treatment, midpoint, and immediate post treatment for determination of clinical improvement.

To determine the impact of NFB, the following assessment tools (see Table 4) will be administered at baseline, 4-6 weeks (midpoint of treatment), and 8-10 weeks (conclusion of treatment) and 2 months following completion to the control and intervention mTBI groups.

Table 4. Study Surveys & Questionnaires with Reliability & Validity, and their Study Objective(s)*

#	Name of Assessment	Validity & Reliability	Description	Study Objective Addressed
1	Headache Impact Test (HIT-6)	Reliability: Cronbach's Alpha 0.75-0.92 Test-Retest r = 0.78 Validity: r = 0.82	The HIT-6 is a 6-question tool designed to describe and communicate the way people feel and what they cannot do because of their headache. (6 questions, 3 min)	Objective 1. Provide data on the impact of NFB training as compared to control on Veterans' headache impact
2	Insomnia Severity Index (ISI)	Reliability: Cronbach's Alpha 0.74 Validity: r = 0.71	Seven question self-report instrument used to quantify perceived current insomnia. Targets past week's symptoms and daytime consequences consistent with DSM-IV criteria. (7 questions, 5 min)	Objective 2. Provide data on the impact of NFB training as compared to control on Veterans' Quality of sleep
3	QIKtest Continuous Performance Tests (QIKtest)	Reliability: test-retest r = 0.74-0.87 Validity: Sensitivity of 73% and Specificity of 73%	Computerized visual performance test to assess attention and impulse control, speed and consistency of response. Specifically intended for use by neurofeedback clinicians. (21 min – best done in the morning and repeated at same time)	Objective 3. Provide data on the impact of NFB training as compared to control on Veterans' Attention functioning
4	[NIH Toolbox NEUROQOLTBI] - Sleep, Roles, Activities,	A relatively new tool with 14 subscales available – only 5 relevant to this study will be used	a) Satisfaction with social roles and activities-short form b) Ability to participate in social roles and activities- short form c) Positive affect and well-being-short form d) Sleep disturbance-short form	Objective 1, 2, & 4 Provide data on the impact of NFB training as compared to control on Veterans' Quality of sleep and

	Affect & Headache]	Reliability range: α = .91 to α = .98 Validity: r = .78- .89	e) Headache-short form. Combined these 5 scales have a total of 43 questions. (43 questions, 20 min)	frequency, duration, severity of headaches and quality of life.
5	Quality of Life After Brain Injury QOLIBRI	Reliability: Cronbach's Alpha 0.75-0.95 Test-retest r = 0.73. Validity: Sensitivity 75% Specificity 75%	A 37-item instrument consisting of 6 scales measuring cognition, self, daily life and autonomy, social relationships, emotions, and physical problems. Designed to measure quality of life specific for TBI. (37 items, 15 min)	Objective 4. Provide data on the impact of NFB training as compared to control on Veterans' Quality of life related to mTBI
6	General Symptom Inventory (GSI)	Used in clinical practice- was found to be very useful in the ongoing assessment of key symptoms while undergoing NFB sessions	Self-report instrument of symptoms in 7 categories including sleep, attention and learning, sensory, behavioral, emotional, physical, and pain (less than 10 min). [Note: In addition to the assessment schedule, an abbreviated symptom list will be used by neurofeedback specialist at each session to assist with treatment planning.]	Objective 5. Provide data on the impact of NFB training as compared to control on Veterans' General physical, neurobehavioral, and emotional symptoms
7	Depression, Anxiety and Stress Scale – 21 (DASS21)	Reliability: Cronbach's Alpha 0.93 Validity: r = 0.73-0.85	DASS21 is a set of three self-report scales designed to measure the negative emotional states of depression, anxiety and stress. (21 items, less than 10 minutes.)	Objective 5. Provide data on the impact of NFB training as compared to control on Veterans' General emotional symptoms
8	Demographic Data Form	No validity or reliability data available	Age, gender, all current medical diagnoses, relevant symptoms to study, all current medications, current therapeutic classes & treatments, medical board status and previous experience with biofeedback. (2-10 min)	Objective 5. To assess variables impact on treatment (also determination of initial eligibility to participate in study)
Additional Baseline Instruments				
9	Patient Health Questionnaire-9 PHQ-9	Reliability: Cronbach's Alpha 0.96 Validity: r = 0.62-0.90 p<.001	PHQ-9 is a nine-item depression self-report module from the full Patient Health Questionnaire. Scores range from 0-27. (9 items, 2-5 min)	Objective 5. To determine the presence of an often co-occurring health issue, depression, with mTBI prolonged symptoms. Estimates as high as 34% of mTBI SMs with depression.
10	Posttraumatic Stress Disorder Checklist PCL-5	Reliability: Cronbach's Alpha 0.89 Validity: Sensitivity 84% Specificity 72%	The PCL-5 is a 20-item questionnaire, corresponding to the DSM-5 symptom criteria for PTSD. The wording of PCL-5 items reflects both changes to existing symptoms and the	Objective 5. To determine the presence of an often co-occurring health issue, PTSD, with mTBI. Estimates as

		r = 0.89	addition of new symptoms in DSM-5. (20 items, 5-10 min)	high as 60% of SMs with mTBI with PTSD.

Table 5 depicts the schedule of administration for each of the tools used in this study.

Table 5. Assessment Tool Schedule of Administration by Group							
Assessment Tool			**Schedule of Administration**				**Group**
No	**Abbreviated Name**	**Initial: at -1 week**	**Mid: at 4-6 weeks [±1 week]**	**End: at 8-10 weeks [±2 weeks]**	**2-Month Follow-up**	**Other**	**Intervention and Control**
1	HIT-6	x	x	x	x		x
2	ISI	x	x	x	x		x
3	QIKtest	x	x	x	x		x
4	NEUROQOL TBI	x	x	x	x		x
5	QOL ABRI	x	x	x	x		x
6	GSI	x	x	x	x	At each session*	x
7	Demographic Data Form**	x	x	x	x		x
	Additional Baseline Instruments						
8	PHQ-9	x	x	x	x		x
9	PCL-5	x	x	x	x		x
10	DASS-21	x	x	x	x		x
	***** An abbreviated symptom inventory based on participant's primary symptoms will be administered at each NFB session to assist with treatment planning. **Current medications, diagnoses, and treatments that were indicated initially on Demographic data will be checked at the 3 assessment sessions to see if any deletions or additions occurred during course of study intervention.						

Pre-Enrollment and Enrolled Procedures: The pre-enrollment procedures include a consenting visit and initial baseline assessment session. Once enrolled, the participants will begin their randomized intervention or control procedures and will receive 3 additional assessments at 4-6 weeks and 8-10 weeks and a 2-month follow-up. To avoid any potential bias or investigator influence, a research nurse coordinator or research assistant will conduct all assessments. See Table 6 for pre-enrollment and enrolled procedures timeframes.

Table 6. Schedule of Study Procedures						
Pre-Enrollment		**Enrolled Participants**				
Consenting	**Randomization**	**Assessments**				**Groups**
-1-2 weeks	-1 week	Baseline 0 weeks	Mid: at 4-6 weeks **[±**1 week]	End: at 8-10 weeks **[±**2 weeks]	Follow-up at 2-months	Intervention and Control

Consenting Visit: All eligible potential participants will be screened for suicide intent and consented and will fill out a contact information form. Contact information will be obtained in order to send or call in reference to reminders of appointments and assessments. The last four digits of the enrolled participant social security number will also be collected to enable proper charting procedures in the electronic health record. If participant agrees on consent that contact information may be saved for possible future research studies, all contact information will be saved on a secured server in a password protected file. Participants will be informed that all forms and questionnaires used in this study will have a unique identification (ID) number that will be associated with a participant. A master list that associates the patient's name and ID number will be kept by the PI in a locked secure environment and be maintained in accordance with the Records Control Schedule

(RCS) for Research Records 10-1, Para 7.6 Research Investigator Files which indicates that files and data can be destroyed 6 years after cutoff (cut off will occur at the end of the fiscal year after closure of the research project). An Initial Baseline Assessment Session visit will be scheduled after the participant is consented.

Consenting Procedures:

An informed consent process for this study which is designed to be a minimum risk study will take place in a private conference or office room at the VAPIHCS site. Consenting process will be conducted by a member of the research team following strict script guidelines to offset any potential for coercion or misinformation. Initial overview of study may be done in small group settings (up to 10 potential participants) or individually. The consent will be written on a 6th grade level in the description of all aspects of study. The consent will be thoroughly reviewed individually with each potential participant before he or she signs the consent. The participant will also be asked to review and sign a HIPAA Authorization Form. Only the participant can sign his or her consent and HIPAA Authorization Form. Time will be allotted for questions and answers. In addition, potential participants will be encouraged to discuss participation with family member(s), friend(s), and/or health/legal professional(s) if desired. The potential participants will be instructed that if they want to participate, they should make an appointment for a consenting visit. If they wish to participate at a later date they can contact the investigator at a later time. All signing of consents will be done on a one to one basis to assure all questions have been answered to the potential participant's satisfaction. The research team member will use a Teachback process (asking participant to summarize a paragraph just discussed and write out one sentence) to ascertain the ability to comprehend consent form and ability to read, write and follow directions. During the consenting session, because the Veterans with mTBI who are experiencing chronic PCS may be at risk for suicide, they will be screened for suicide intent using the C-SSRS secondary screen. If a positive screen is obtained (indicated by a yes to questions 3, 4, 5, or 8) the consenting process will be stopped. The following will occur depending on Veteran preference/need: Veteran will be walked over to the Ambulatory Care Clinic Mental Health front desk for triage, the 24-hour crisis hotline called (1-800-273-8255 or 988) or 911 called if there is imminent danger. A copy of the signed consent document will be given to each participant. No study procedures will occur prior to the participant giving informed consent. All members of the research team consenting potential participants will have completed Citi Training for good clinical practice.

At the end of the consenting process, participants will be randomized into one of the study groups (NFB or Control). Those participants assigned to the intervention group will be scheduled for the initial, 4-6-week, 8-10-week and 2-month follow-up assessments as well as for the 10 weeks of intervention sessions: up to 5 1-hour (but usually 3) NFB training sessions a week. Participants assigned to the control group will be scheduled for 4-6-week, 8-10-week and 2-month follow-up assessments.

Communication with Participants: Study staff will contact enrolled participants via multiple methods including, face-to-face communication, telephone call, mailings (e.g., US postal service), electronic mail (e-mail) and My Health*e*Vet Secure Messaging. Participants will have the option to use any, all, or a combination of the communication methods. Participants are generally contacted for appointment reminders, gift card disbursement, or other research-related information. All ORD guidelines regarding the use of electronic mail and My Health*e*Vet secure messaging will be followed. Research staff will be careful with the frequency of contacts to participants to avoid any perceived coercion or harassment. Electronic and mailed communications will be saved in accordance with the VHA Record Control Schedule (RCS 10-1).

For e-mail communication, a study-specific Outlook mailbox account or other appropriate research staff Outlook account will be used to send and receive messages. All necessary precautions will be put in place to not transmit PII/PHI to participants and to not identify the research study. Generic, standard Subject lines will be used to not disclose any PII/PHI. For example, appointment reminders will use the subject line, "Appointment Reminder." See Appendix A for example phrases for e-mail use.

For My Health*e*Vet Secure Messaging, a study-specific group will be created for use in the study. Although VA sensitive information is allowed with secure messaging, research staff will use the least amount of PII/PHI information necessary in the message. See Appendix A for example messages for My Health*e*Vet Secure Messaging use.

Volunteer identification and confidentiality: Participants will not be identified in any presentation of the results. The initial form with contact information and last four of the participant's SS# that will be used for appointment, reminders and charting purposes will be kept in a locked file cabinet in either E-wing 4A-100 or

the Airport Industrial Park (AIPA) Suite 401A and in the research projects file on the VA server (\\R01HONhsm01.r01.med.va.gov\ R:\Project Files\Research-JC-NFB-0003) and destroyed at completion of the study unless the participant indicates on the consent form that we can recontact for future studies. A master list that associates the patient's name and ID number will be kept by the PI in a locked secure environment and be maintained in accordance with the Records Control Schedule (RCS) for Research Records RCS10-1, Para 7.6 Research Investigator Files, which indicates that files and data can be destroyed 6 years after cutoff (cut off will occur at the end of the fiscal year after closure of the research project). All hard copies of research questionnaires will be stored in a locked secure environment in Room 4A-100 in E-wing or in AIPA Suite 401A and maintained in accordance with the RCS. All electronic data related to the questionnaires and demographic data will be stored on a Region 1, secure platform. However, this information may be used for relevant future research if participants agree on consent form and the IRB approves the new study. Complete confidentiality cannot be promised because certain information bearing on participant's welfare may be required to be reported to appropriate authorities.

Data use in future studies: The de-identified study data from the assessment forms only could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the participant if the participant agrees to this on the consent form and HIPAA Authorization Form. The PO will certify the dataset as fully de-identified before stored on the project's R:\ drive folder.

In addition, the participant contact information will be kept for future possible relevant studies if the participant agrees to this on the consent form. Only the investigators on this present study will have access to the information. If a new study has as part of its plan to determine the long-term effects of NFB, the potential participant will be contacted to see if he or she would like to participate in this new study. The new study would need to be approved by the Institutional Review Board, which reviews all new studies. All contact information will be kept on the project's R:\ drive folder.

Participants can rescind their consent about their study information and contact information for future study use at any time upon communication with the primary investigator. If participants agreed to have their de-identified data kept for future use, but later rescind this consent, these data cannot be removed since they are de-identified and no linkages are possible.

Informed Consent Ability: The population for this study will not include individuals that cannot provide informed consent.

Assent: Not applicable to this population. No children are included in this study.

Randomization - Assignment Process into Control or Intervention Groups: A blocked randomization schedule will be created at the beginning of the study with randomly selected block sizes of 4. The randomized block size will prevent study personnel from predicting treatment assignments for potential participants. The individual assignments of the randomization schedule will be placed in sequentially numbered opaque envelopes that will only be opened as new participants are enrolled into the study

Enrollment: Enrollment will be completed when the potential participant is randomized into one of the study groups.

Study Procedures for Enrolled Participants

Initial Baseline Assessment Session Visit (approximately 2.5 hours): Participants will be given preparation instructions to ensure optimum test results and will be instructed to have adequate rest the night before and to have eaten a regular meal or snack prior to the test session. There will be an attempt to schedule assessment session during the period when they report maximum alertness. One of the tests, the attention QIKtest will be administered early in the assessment session to minimize test fatigue. The participants will also complete several other questionnaires (see Table 5) during this baseline visit in addition to the demographic form will include pregnancy status (or plans to become pregnant in the next five months) co-morbid health issues, description of headache, insomnia, and attentional disorder, experience with biofeedback, and participation in co-occurring classes or therapies, list of current medications, and ethnicity. Although the total time for completion of the questionnaires is estimated to be 120 minutes, a 2½-hour time frame is given for rest

periods, water break, slow test takers, and the answering of any questions the participants may have. Assessment session visits will be conveniently scheduled.

Mid (4-6-week), End of Treatment (8-10-week) and 2-Month Follow-up Assessment Sessions (2.5 hours each session): As above in the baseline assessment, participants will be given preparation instructions to ensure optimum test results. Participants will be instructed to have adequate rest the night before, and to have eaten a regular meal or snack prior to the assessment sessions. There will be an attempt to schedule all sessions at the same time of day for each individual participant, during a period of maximum alertness. One of the tests, the attention QIKtest will be administered early in the assessment session to minimize test fatigue. The participants will also complete several other questionnaires (see Table 5) during these 3 assessment sessions. In addition, the participants will indicate any changes on the demographic form, including changes in pregnancy status (or plans to become pregnant in the next five months) co-morbid health issues, participation in co-occurring classes or therapies and medications. Although the total time for completion of the questionnaires is estimated to be 120 minutes, a 2.5-hour time frame is given for rest periods, water break, slow test takers, and the answering of any questions the participants may have. Should a participant be unable to complete any assessment visit in person, the questionnaires may be mailed to the participant and mailed back at no cost to the participant. Decision to mail the questionnaires will be made by the study team on a case-by-case basis. The QIKtest cannot be mailed therefore this missing data point will be accounted for statistically at final analysis. Instructions will be mailed with the packet. See Appendix B for an example of the general information to be sent to the participants.

Participation Termination by the Principal Investigator: Possible reasons for study participation termination by the PI without concurrence by the participant include: concern for the individual's health and/or safety and participant non-compliance with study procedures (e.g., excessive number of missed NFB and/or assessment appointments; non-responsive to outreach attempts for rescheduling; non-responsive to control group phone calls.) Participants will be informed of this decision either in person, via telephone, or via letter. Participants who are terminated could enroll at a later date if they desire. However, the research team will review these requests on a case-by-case basis.

Statistical and Data Analysis Plan

The analyses will be conducted based on intention-to-treat principle (Friedman, Furberg, DeMets, 2010) where participants are analyzed according to their group assignment regardless of the treatment received (e.g., switching treatments or poorly adhering to assigned treatment). Patient demographics will be presented using frequencies and percentages for categorical variables and means and standard deviations for continuous variables. Although balance between intervention arms will be guaranteed by randomization, there may be unmeasured confounding. Two sample t tests or chi-square tests will be conducted to investigate potential confounding effects on demographic variables.

For each hypothesis, first two sample t-tests will be utilized to assess the effect of NFB intervention at each time. Then, a repeated-measures analysis of variance (ANOVA) will be implemented for the outcome variable that shows significant group effect. The mixed effects model will include group (between-factor), time (within-factor), and the interaction between group and time as fixed effects. From this model, the interaction will allow the testing of whether longitudinal trajectory is associated with group assignment. The longitudinal trajectory from baseline, 4-6-week and 8-10-week to 2-month follow-up, for each outcome of interest will be investigated in this model accounting for covariance structure (e.g., AR(1)) within participants. This determines the rate of improvement during the course of the intervention. Any baseline subject characteristics found to differ between groups as covariates to assess the impact of the baseline covariates on the effectiveness of the intervention over the course of the study will also be included if needed].

The outcomes of interest for each hypothesis are clinically significant:
1) Reduction in frequency, severity and/or impact of headaches: HIT-6 and NEUROQOLTBI
2) Improvement of perceptions of quality of sleep and insomnia severity: ISI and NEUROQOLTBI Sleep disturbance
3) Improvement in attention function: QIK-Test
4) Improvement in the quality of life: QOLIABRI and NEUROQOLTBI Satisfaction & Participation in roles and activities

5) Improvement in the general physical and emotional symptoms: GSI, DASS21, PHQ9, PSL-5 and NEUROQOLTB Positive affect and wellbeing.

As a secondary analysis, a per-protocol analysis will investigate the effect of the intervention in participants that adequately adhere to the intervention, e.g., participants that attend over half of the treatment sessions versus participants attend less half of the treatment sessions. For all analyses, model assumptions will be evaluated with graphical and formal statistical tests such as Kolmogorov-Smirnov goodness-of-fit test. If there is marked nonlinearity or non-normality, transformation of the dependent variable or using a different link function such as the log link function will be considered. All analyses will be done in SAS version 9.4 on a non-VA Computer with two-tailed tests and P-value < 0.05 will be considered statistically significant.

Other statistical analyses not run by the biostatistician will be completed by the research team within the VA Informatics and Computing Infrastructure (VINCI) workspace.

Power: Power: Literature on NBF studies of patients with TBI have reported dropout rates ranging from 10% to 30% (Nelson & Esty, 2012; Zoeful, Huster, & Herrmann, 2011). Assuming a dropout rate of 28% and a moderate autocorrelation of 0.6 among repeated measures, this sample size will ensure to detect at least significant difference of 0.49 standard deviation with a power of 80% in the NFB intervention group compared to the control group with two-tailed significance level of 0.05 based on Diggle's et al (2002) approach for 4 repeated measures. This indicates that differences of less than 15% can be detected for HIT-6 (5.8% based on Cerritelli, 2015) and QOLABRI (13.8% based von Steinbuechel et al, 2016) and less than 26% for ISI (17.9% based on Nguyen, 2017) and DASS21 (19.7% based on Arundine et al., 2012) questionnaires. Thus, differences of 15% to 25% in the study instruments would be clinically significant. In addition, this study will detect a difference of at least 0.67 standard deviation if multiple testing is adjusted using FDR, which also provides a moderate effect size.

Potential Benefits to Participants:

The benefits to the subject could include: For the participants receiving NFB, benefits may include a decrease in the number and severity of headaches, enhanced sleep, and attention ability and an overall perception of enhanced quality of life. In addition, the participant may experience enhanced positive emotions. Indirect benefits include the knowledge that the participant has contributed to the body of knowledge relating to the efficacy of NFB. There may be no direct benefit to volunteers.

Risk-Benefit Ratio: The risks of this project are designed to be minimal, and there are several safeguards in place that will minimize any associated risks related to this study.

Potential Risks to Participants:

The risk to volunteers in this study is designed to be minimal. Because this intervention is a personal biofeedback process, whereby the participants are training themselves based on their own physiological parameters, no serious adverse event is anticipated or expected. Anticipated and not serious brief side effects such as anxiety, a tightness in muscles, stomach discomfort, or mental cloudiness may be experienced but are expected to go away within minutes. Most people feel relaxed and calm during and after NFB training.

As mentioned earlier, each person has a particular setting on the equipment that the person's brain prefers. Until the NFB specialist finds that particular setting, although unlikely, it may be possible that some symptoms may feel a little worse when the individual goes home or the next day. This is not bad news since it informs the NFB specialist more about a person's brain and the particular setting that a brain prefers can be found more quickly. The NFB specialist can always find that setting especially with the individual's help by letting the NFB specialist know how they are feeling. In very little time, a NFB specialist can find that setting, and any symptoms the individual was experiencing before the study may begin to get better. If this occurs at all, it is usually very short-term, not usually more than a minor discomfort, and easily adjusted.

Although some adverse events have been published in the literature relating to NFB, they were either related to a study involving the use of arbitrary non-individualized settings (essentially using sham techniques) (Rogel et al, 2015) or an article that outlined off-hand comments made by a few practitioners on list groups who were seeking guidance from other practitioners about issues experienced while conducting NFB. The practitioners themselves were not informed that their comments were to be published. The actual skill or previous training of these practitioners was not indicated, nor were there case-studies of the patients or protocols discussed

(Hammond & Kirk, 2007). Although no adverse events were ever experienced in the private practice of the PI, any unexpected or serious adverse events will be reported to the VAPIHCS IRB. The event will be categorized (mild, moderate or severe) with its relationship to the study indicated (e.g. definitely related, probably related, possibly related, unlikely related, unrelated). The investigators will evaluate each adverse event. Any adverse event previously documented will be recorded as "ongoing," "improved," "resolved" or "worsened" as appropriate. If an adverse event changes, or advances in quantity or quality, a new IRB report and record of the event will be initiated and the old adverse event will be ended.

Risk Level: The study is designed to have a risk level of minimal, in that the probability and magnitude of harm or discomfort anticipated in the research is not greater than that ordinarily encountered in daily life of during the performance of routine physical activity or psychological examinations or tests.

Physical Risks: We do not anticipate any risk of physical harm as a result of participating in the study.

Risk of Emotional Upset: The risks of the proposed study are believed to be minimal. Some participants might experience some concern about anonymity. The research team will be available during or after the data collection to answer address any concerns a participant might have regarding this issue and strong data safety procedures are being implemented to protect participants' anonymity.

Social, Legal, and Economic Risks: The study does not discuss information on protected topics. Participants will not be personally identified in any reports or publications that may result from this study.

Financial Obligation: There will be no cost to participants for any treatment received as part of this research study. Some Veterans are required to pay a co-payment for medical care services provided by the VA. This co-payment requirement will continue to apply to medical care and services provided by the VA or community provider that are not a part of this study.

Therapeutic Risk and Research Risk: There are no known research risks in this study. It is a training biofeedback program.

Vulnerable populations: There is a possibility that a Veteran who may be economically disadvantaged may be enrolled. However, because this study offers no financial incentives, there is no financial coercion that would require additional safeguards for the economically disadvantaged. Additionally, the economically disadvantaged is not a group that is targeted for this study. If a woman becomes pregnant while participating in this study, she will be removed from active engagement with an intervention but will be followed through the course of the study and will complete the assessments.

Risk Management Overview:

Crisis Procedure: Relevant to risk for harm to self or others and suspected abuse or neglect of vulnerable persons, participants are informed in the Informed Consent Procedures that these are circumstances in which confidentiality is not protected. In addition, if a participant(s) has to be terminated from the protocol due to safety concerns, the study team will explore resumption of therapy with any referring clinician and facilitate resumption of therapy through discussion with the therapist (with the client's consent). If there is no referring clinician and there is the need for referral, we will provide referral resources for the participant(s). In situations of imminent threat to self or others occurring at the VA, study staff will dial 911 for emergency assistance from Honolulu Emergency Services.

Civil Reporting Requirements: Regarding suspected abuse or neglect of vulnerable persons, including children, any suspected abuse or neglect of these individuals will immediately be reported to the Department of Human Services, Social Services Division. Study staff, with Dr. Carlson, will encourage the participant(s) themselves to contact the Department of Human Services, Social Services Division to report suspected abuse/neglect, with the study staff present. If they are unwilling to do this, Dr. Carlson and the relevant study staff will make such mandated report and inform the participants of this reporting. To make a report in cases of adult vulnerable populations, study staff will telephone the Department of Human Services, Social Services Division, Adult Protective Services on Oahu at (808) 832-5115 (24 hours). To make a report in cases of suspected child abuse, study staff will telephone the Department of Human Services, Social Services Division, Child Welfare Services on Oahu (808) 832-5300 (24 hours). If reporting is required, the PI or Research Staff will coordinate with the VAPIHCS Privacy Officer or VAPIHCS Release of Information (ROI) staff to ensure proper tracking of the notification in the ROI software.

Safety Monitoring Board: This study will be monitored by the Clinical Science Research and Development (CSR&D) Data Monitoring Committee as required by the CSR&D Merit Award procedures. Weekly meetings among staff will occur to address any treatment or data issues that may arise. All personnel will contact PI immediately upon recognition of safety issue.

Unanticipated Problems Involving Risk to Participants or Others (UPR) Reporting: The PI will assure that all research team members are properly trained in the reporting of UPRs. The PI and research team members will follow policies and procedures in the IRB Scope of Practice. Research staff should report all UPRs experienced by research participants to the study's PI for review. The site's procedures for notification include: (1) verbal notification of UPRs directly to the PI and documentation of the discussion, and/or (2) providing a written notification or report to the PI, which will be on a case report form, sponsor communication, study site UPR reporting form, progress note, email, or other method deemed acceptable by the PI. The PI or designee will report all UPRs to the IRB.

Adverse Event (AE) Reporting: According to VHA Handbook 1200.05, an AE is defined as any untoward physical or psychological occurrence in a human subject participating in research. An AE can be any unfavorable or unintended event including abnormal laboratory finding, symptom or disease associated with the research or the use of a medical investigational test article. An AE does not necessarily have to have a causal relationship with the research, or any risk associated with the research or the research intervention, or the assessment. However, to become a serious adverse event, the AE must be unanticipated, serious and study related. VHA Handbook 1058.01 provides definition guidance.

Any serious adverse event or serious UPR becomes reportable in accordance with the provisions of the VAPIHCS Standard Operating Procedure. Adverse events and UPRs that do not qualify as serious will be summarized and presented to the IRB at the time of Continuing Review. Within 5 business days of becoming aware of any serious unanticipated problem involving risks to subjects or others in VA research, the PI will ensure that the problem has been reported to the IRB in writing. Within 5 business days of becoming aware of any apparent serious or continuing noncompliance, the PI will ensure that the issue has been reported to the IRB in writing. Within 1 hour of becoming aware of any unauthorized access to VA sensitive information or an incident that impacts, inhibits or compromises network security, the PI will ensure that the situation has been reported to the facility Associate Chief of Staff of Research & Development, facility Information Security Officer and Privacy Officer. Within 2 Hours of becoming aware of an SAE that has potential media, congressional or litigious implication at a facility, the IRB must be notified and the VA facility Director must ensure that VISN 21 Director is notified.

Safeguards: This study has been designed with several safeguards. These include: (a) using exclusion and inclusion criteria that will identify appropriate patients for this treatment (b) requiring an on-site licensed health care personnel be available during any clinical contact in the case of a clinical emergency and (c) strict data handling procedures to manage personally identifiable information (PII) and personal health information (PHI). Participants will also be informed of any new significant findings developed during the research that may affect their willingness to continue participation.

Reporting Protocol Deviations: The PI will assure that research team members are properly trained in reporting of any deviations to the protocol. Research team members will report protocol deviations to the study's PI and the PI or designee will notify the VAPIHCS Research Committee Coordinator for potential IRB review. Any deviations to the protocol that may have an effect on the safety or rights of the participant or the integrity of the study will be promptly reported to the IRB and Human Research Protection Office. The site's procedures also include: documenting protocol deviations, if appropriate, via progress note, email or other method deemed acceptable by the PI.

Data and Safety Monitoring Plan

This study will be monitored by the Clinical Science Research and Development (CSR&D) Data Monitoring Committee as required by the CSR&D Merit Award procedures.

Identifiers: During the study, names, telephone numbers will be maintained to be able to contact participants for appointment reminder purposes. The day before each appointment, the participant will be called as a reminder. All surveys, data information sheets, diaries collected will have a unique identifier starting with 1-100, 1-101, 1-102 ... ending with 1-200. A master list that associates the participant's name and ID number will be

kept electronically in a password-protected file saved on a secure VA server and be maintained in accordance with the Records Control Schedule (RCS) for Research Records 10-1, Para 7.6 Research Investigator Files, which indicates that files and data can be destroyed 6 years after cutoff (cutoff will occur at the end of the fiscal year after closure of the research project). All data will be de-identified for analysis.

If there is any question as to what may constitute identifiers or identifiable information, the VA Pacific Islands Health Care System (VAPIHCS) Privacy Officer (PO) will be consulted. Any personal identifiers collected, such as age, diagnosis(es), ethnicity or the last four digits of social security number will have to be approved by the VAPIHCS Informational Security Officer (ISSO) and VAPIHCS IRB and be included in a formal consenting process with the participants.

Confidentiality: The master list with the participants' names and their unique identifiers will be kept electronically in a password-protected file saved on the project's R:\ drive folder. The participants' names and contact information will also be kept when not in use in the locked file cabinet. The project staff will have access to contact information. In addition, representatives of the VAPIHCS IRB are eligible to review study records. Hard copy information to be collected includes informed consent documents, the HIPAA Authorization Form and assessment data. The physical files containing PII/PHI (e.g., consent forms) will be stored separately from physical files that contain non-identifying information (e.g. assessment data), which will be identifiable only with a study specific ID number.

Collection of Social Security Number (SSN): No real, full SSN will be collected in this study. The last four numbers of Veterans' SSN will be collected on the participant's contact information sheet as well as kept in a secure electronic recruitment database to aid in record keeping and matching Veterans to their VA records due to possibility of more than one Veteran having the same name.

Information Security Training: With regard to monitoring of data quality and PHI, all required project team members will complete the required VA Privacy and Information Security Awareness and Rules of Behavior training, which include information about maintaining data integrity and security.

Data Access: Procedures for this study require access to several systems.

Veterans Health Information Systems and Technology Architecture (VistA): The Computerized Patient Record System (CPRS) will be most frequently used VistA system in this study. CPRS is the electronic health record for Veterans. Procedures for general access and continued use of CPRS are guided by Facility policy. For research-related use, study staff are given authorization to enter participants' charts after the consent form is signed and they are officially enrolled into the study. CPRS access will be active until study closure. This is needed in case of any question from outside entities. However, continued access to CPRS after study closure will be informed by the individual employee's duties (e.g., if study staff is also clinical staff). In the event study staff formally separate from the facility, CPRS access is revoked upon execution of facility-related separation procedures. All study staff are expected to operate under the least privilege concept; for example, when a participant has completed active study procedures and all notes are entered, the record/chart does not need to be accessed.

VA Network Drive Assigned Research Project Folder (R:\\R01HONhsm01.r01.med.va.gov\ R:\Project Files\Research-JC-NFB-0003): Access to the R:\ drive project folder is provided to study staff assigned to the protocol to carry out all project-related duties and procedures. Access to the research project folder is granted by the Research and Development Administrative Officer (AO) after the staff member's SOP is executed. The AO is also responsible for revoking folder access. Permission and revocation is requested by the PI or their designee. Access is revoked when a study team member leaves the project. Active study staff will verify with the AO that permissions have been removed. At study closure, study staff will follow RCS 10-1 guidelines regarding R:\ drive access and disposition.

VA Informatics and Computing Infrastructure (VINCI): Access to VINCI is provided to research staff assigned to the protocol so that they can access this server for data analyses (see VINCI section below). Permission to VINCI workspace is granted by VINCI concierge services and access to the workspace is launched at https://vincicentral.vinci.med.va.gov/SitePages/Workspaces.aspx. At the conclusion of the study, study staff will follow VINCI procedures to close the project space and follow data disposition procedures outlined above.

Data Protection: Although laptop computers are utilized, they are part of an NFB special use system that will remain tethered to its workstation for use on VAPIHCS Honolulu station. An I-Phone hotspot will be used as a wireless device to transfer the QIK test data from the stand-alone computer used for NFB on which the QIK Test resides to an offsite program. The QIK Test data will have no identifiers other than the study ID and the decade of birth. The stand-alone NFB special use system resides on a specialized computer only used for the administration of NFB and QIK-Test. Regarding the NFB special use system, no identifying data of any kind is stored. The NFB special use system is password protected. During the course of this study, no VA sensitive information will be removed from VA protected environment. As of March 2025, the NFB special use system and offsite program are not used as participant procedures are complete.

The biostatistician will receive de-identified data only that has been verified by the PO. Further, no identifiable data will be placed on a laptop computer, stored on the hard drive of the desktop computer or stored or transferred on portable media such as CDs or disks.

Data Flow: The PI will coordinate the management of data collection, data flow, data entry, and data quality assurance. The study protocol will be approved prior to recruiting or consenting any participants. A dedicated database with extensive edit and reliability checks will be developed for this project. Assessment and questionnaire data will be entered by hand into an electronic database under the supervision of the PI and study coordinator and stored in the project team folder on the VA server (\\R01HONhsm01.r01.med.va.gov\ R:\Project Files\Research-JC-NFB-0003). Data quality will be monitored on a continuing basis. All raw data will be visually inspected by the project staff prior to data being entered. Consistency check for reliability of data entry will be part of a routine data cleaning procedure. Any discrepancies will be presented to the PI or Co-Investigator who will make final decisions about data. Identifiable information may only be saved to a VA server, never a laptop or desktop computer. Data will be retained in accordance with RCS 10-1; disposition cutoff will be at the end of the fiscal year after completion of the research project, and the retention period is records will be destroyed 6 years after cutoff.

Data Capture, Verification, and Disposition: Study data will be captured using the Excel program saved to secure VA servers. It allows secure and easy access and convenient data tracking. It also allows easy exporting of data to common statistical packages. The project staff will develop data collection files with proper branching logic and stop actions and the data will be entered. The PI and study coordinator will monitor data submitted on a regular basis for quality control purposes. They will communicate with project team to resolve any database access and data entry issues as soon as they are discovered. Auto-validation steps and rules will be built into the database to reduce data entry errors. Steps include range checks and double data entry to detect data entry problems (omissions, errors, duplicate and inconsistent data) and to identify data outliers and extreme values. Any suspicious values found will be further investigated and necessary recovery and corrective steps will be taken and documented, after appropriate backup of the existing dataset. An audit trail will track changes. Reports on data quality and timelines, as well as participant recruitment, accrual and retention, will be easily available to the PI and biostatistician.

Data will be maintained in accordance with the RCS 10-1, Para 7.6 Research Investigator Files, electronic files will be stored in a study folder located on a secure VA server that is accessible only by the PI, Co-Investigator, Associate Investigators, Research Assistant, and Research Coordinator.

The PI or designee will immediately report any incident of theft, loss, or compromise of VA sensitive information, VA equipment or device, or any non-VA equipment or device used to transport, access, or store VA information, to the ISSO and/or PO and supervisor. Within 1 hour of becoming aware of any unauthorized access to VA sensitive information or an incident that impacts, inhibits or compromises network security, the PI will ensure that the situation has been reported to the VAPIHCS Associate Chief of Staff for Research, VAPIHCS ISSO and PO. The ISSO or PO will promptly report the incident (within one hour) using the PSETS system. in accordance with the Incident Management procedures. If the PI leaves, the Associate Chief of Staff for Research or the Admin Officer will ensure rights are properly removed within the required 24-hour period, per VA 6500.

VINCI

De-identified data from the assessment visits may also be uploaded to the VA Informatics and Computing Infrastructure (VINCI) for other analyses.

Research study staff use an audited VINCI upload file utility to move de-identified data into VINCI servers for analysis and the download file utility to move summarized statistical reports from VINCI servers to network storage. VINCI will not be provided to any external entity.

VINCI primarily serves as the platform to access the VA's Corporate Data Warehouse. However, research scientists can upload their own study data for data analysis within the VINCI environment. VINCI offers several statistical software packages to analyze data. All VINCI policies and procedures will be followed by all research study staff. At the conclusion of the study, study staff will follow VINCI procedures to close the project space and follow data disposition procedures outlined above.

Flagging Medical Records of Participants: The PI does not intend to flag the participants in the study.

Importance of Knowledge

This project will be an important step towards the broad clinical implementation of an evidence-based treatment solution for Veterans experiencing chronic headaches, insomnia and attention disorders. This study directly maps onto VA initiatives focused on enhancing Veteran's access to evidence based non-invasive and non-pharmacological treatment options. Also, because of the ethno-culturally diverse population in Hawai'i, results can inform VHA providers about the use of NFB among diverse groups of Veterans, including Asian American and Native Hawaiian/Other Pacific Islander Veterans not often adequately represented in other studies. NFB is not widely used in the VA, therefore the results will be highly relevant to VA clinicians, administrators, and policy makers nationwide who seek effective non-invasive treatment options. Results can guide future full clinical trial studies on use of NFB in relation to current best practices for care of Veterans in relation to other issues experienced by Veterans, i.e. PTSD, Pain, etc. Dissemination activities will target a broad audience and will include: (1) a one-sheet summary abstract, (2) web-based fact sheets for several VA venues, (3) manuscripts and publications for both professional and non-professional channels. The publications stemming from this research project will be made available to the public through the National Library of Medicine PubMed Central website within one year after the date of publication. Costs for producing the dissemination materials will be minimal. The investigators will also deliver local and national presentations at VA and academic professional conferences. Finally, long term research results can assist in the future development effective NFB protocols that can be potentially implemented in VA clinical settings and disseminated directly to clinical settings via existing infrastructures established by this research team.

APPENDIX A

E-mail and My HealtheVet Message Examples

*note: this is not an exhaustive list.

POSSIBLE SUBJECT LINES: Visit Reminder, Gift Cards, Please Call

1. VISIT REMINDER Message:

Reminder: You have a visit on DATE at TIME. Please call 808-433-3316 if you need to reschedule or have questions.

Thank you.

2. GIFT CARD Message

Here are the gift cards owed to you and associated visit dates. If you have questions, please call 808-433-3316.

DATE	VISIT TYPE	GIFT CARD NUMBER
MM/DD/YYYY	ASSESSMENT (or appropriate abbreviation)	XXXXXXXX
	TREATMENT (or appropriate abbreviation)	

IMPORTANT! Please reply to this email to confirm receipt of these cards.

Thank you.

3. CONTACT OFFICE Message:

Our team has been trying to contact you. Please call our office at 808-433-3316.

Thank you.

*the following is the closing for all e-mails:

SIGNATURE BLOCK (no study-related information included)
Research Staff Name
Contact Information

Email is not secure. Please do not reply to this message with any personal information or personal health information. Please call 808-433-3316.

APPENDIX B

General instructions for mailed assessment questionnaires

Aloha! Thank you for taking the time to complete these questionnaires for our Neurofeedback study.

Instructions:
Please complete all questionnaires in one sitting, away from distractions. They can be completed in any order. Read and answer each item. Do not spend too much time on any item. There is no right or wrong answer. Use a pen and mark your responses clearly. If you change an answer, please initial your correction.

Some people become uncomfortable when asked about their stress or psychological wellbeing. You are free to skip any item you wish not to answer. If you need crisis support, please contact the Veterans Crisis Line at 988 or 1-800-273-8255 and press "1."

IMPORTANT: please write the date you completed the questionnaire on top of the form.

Upon completion, please return all forms in the postage-paid envelope.

If you have any questions or concerns about the questionnaires or the study, please call us at 808-433-3316 or email us at VAHONFBCOMM@VA.GOV

	Name of Assessment	**Description**	**Timeframe of Response**
1	Headache Impact Test (HIT-6)	Headache	Past month
2	Insomnia Severity Index	Insomnia	Past 2 weeks
3	General Symptom Inventory	General Symptoms	Past month
4	Patient Health Questionnaire-9 PHQ-9	How much each item bothered you	Past 2 weeks
5	PCL-5	Post-traumatic stress items	Past month
6	Positive Affect and Well-Being - Short Form	Overall well-being	Past few weeks
7	Headache Pain – Short Form 10a	Headache	Past 7 days
8	Sleep Disturbance – Short Form	Sleep	Past 7 days
9	DASS21	How much each item applied to you	Past 7 days
10	QOLIBRI - Quality of Life After Brain Injury (2 pages)	Part 1 – satisfaction Part 2 – difficulty/bothered	Past 7 days
11	Ability to Participate in Social Roles and Activities – Short Form	Ability to Participate in roles & activities	Past 7 days
12	Satisfaction with Social Roles and Activities – Short Form	Satisfaction with roles & activities	Past 7 days