# Application for Expedited or Full Board Review

**Institutional Review Board**
**Office of Research Compliance**

Please submit this completed form, along with finalized copies of all recruitment materials (e.g., telephone scripts, fliers, etc.), tests, surveys, interviews, and copies of human participants training completion certificates for all investigators and key personnel to the IRB. This training can be found at http://www.utdallas.edu/research/orc/irb/required_training/.

If you require further assistance in completing this form or need additional information, please contact Office of Research Compliance at extension 4575 or by E-mail amanda.boone@utdallas.edu.

**Project Title:** Direct current stimulation for pain treatment in Gulf War Illness

| **Principal Investigator (PI)** | |
|---|---|
| Name (Last name, First name, MI)<br>Vanneste Sven | Highest Earned Degree<br>PhD |
| University Title<br>Professor | Department<br>BBS |
| Campus Phone No.<br>972.883.7277 | E-mail Address<br>sven.vanneste@utdallas.edu |
| Campus Mailing Address | Campus Mail Station<br>CD |
| ☒ Faculty ☐ Staff ☐ Student ☐ Other: | |

| ☐ **Co-Principal Investigator** ☐ **Faculty Sponsor** | |
|---|---|
| Name (Last name, First name, MI) | Highest Earned Degree |
| University Title | Department<br>BBS |
| Campus Phone No. | E-mail Address |
| Campus Mailing Address | Campus Mail Station |
| ☐ Faculty ☐ Staff ☐ Student ☐ Other: | |

| **Primary Contact Person** | | |
|---|---|---|
| Name<br>To Wing Ting | Campus Phone No.<br>9728837275 | E-Mail Address<br>wingting.to@utdallas.edu |

**Other Study Personnel:**

| Name (Last Name, First Name, MI) | Role in Study |
|---|---|
| John Hart, M.D.<br>Jeffrey Spence, Ph.D. | Co-Investigators |
| To Wing Ting, Ph.D. | Study Coordinator |
| Mohan Anusha | Graduate Research Assistant |

Are study personnel outside UTD and its affiliated institutions involved in this study?

☒ **Yes** ☐ **No**

**Non-Affiliated Study Personnel:**

| Name (Last Name, First Name, MI) | Institution | Role in Study |
|---|---|---|
| Haley Robert, M.D. | UT Southwestern | Subcontract PI |
| | | |
| | | |

## Study Funding and Other Support

Is this study funded?

☒ **Yes** ☐ **No**

Please select all appropriate funding sources for this project, including sources of pending support:

- ☒ Federal
- ☐ Industry - For Proft
- ☐ Private - Non Profit
- ☐ Public - State of Texas
- ☐ Public - Local
- ☐ Academic
- ☐ Internal - Departmental

Have all PIs, Co-PIs, and Faculty Sponsors provided a Conflict of Interest Disclosure within the last 12 months? Student researchers should complete and submit the attached Student Conflict of Interest Disclosure along with this application.

☒ **Yes** ☐ **No**

*Please Note: Final approval will be withheld until all Conflict of Interest Disclosures have been received and reviewed by the Office of Research Compliance.*

**Federal Grant Information:**

Granting Agency: Department of Defense

Grant Status:
- ☐ Awarded
- ☒ Pending
- ☐ Not Yet Submitted

Grant Title: Direct current stimulation for pain treatment in Gulf War Illness

Principal Investigator: Sven Vanneste, Ph.D.

## Performance Sites

Mark all UTD affiliated sites where research-related activities will be conducted and the relevant activities performed at each site:

| Performance Site | Recruitment | Procedures | Data Analysis |
|---|---|---|---|
| Richardson Main Campus | ☒ | ☒ | ☒ |
| Callier Campus - Richardson | ☒ | ☒ | ☐ |
| Callier Campus - Dallas | ☒ | ☒ | ☐ |
| Center for BrainHealth | ☐ | ☐ | ☐ |
| Center for Vital Longevity | ☐ | ☐ | ☐ |
| TX Biomedical Device Center - Dallas | ☐ | ☐ | ☐ |

If applicable, please indicate all performance site(s)/institution(s) that are non-UTD affiliated:

| Site Name | Research Related Activity |
|---|---|
| | |
| | |
| | |

Does the non-UTD affiliated institution have an IRB?

☐ **Yes** ☐ **No**

If yes, has IRB approval been obtained?

☐ **Yes** ☐ **No**

Note: A copy of the IRB approval letter is required. If the site/institution does not have an IRB, a Letter of Support/Permission from an equivalent entity or an authorized institutional official may be accepted.

**Which methods will this study include? (check all that apply)**

- ☐ Descriptive
- ☐ Qualitative
- ☐ Quantitative
- ☐ Formative
- ☐ Other, specify:
- ☐ Oral History
- ☒ Experimental/Control Design
- ☐ Ethnographic
- ☐ Longitudinal

## Estimated Study Duration

Please indicate the estimated length of research study:

Three years

## Publication of Results

Please identify all methods in which you may publicly disseminate the results of your study (academic journal, academic conference, a thesis or dissertation for one of your students, etc.).

- ☒ Academic journal
- ☒ Academic conference paper
- ☒ Public poster session
- ☒ Book or chapter
- ☐ Thesis
- ☐ Dissertation
- ☐ Class project
- ☐ Other:

## PROTOCOL SUMMARY

Instructions:

**Use non-professional language** and address each part separately to describe your protocol. Attaching sections of a grant application or proposal is not an acceptable substitute. Provide sufficient information for effective review by all members of the IRB, including non-specialists. Define all abbreviations and terms that are not part of common language.

**Describe the objective(s) of the proposed research:**

Describe why this research project will be carried out. Clearly state the overall objectives, specific aims, hypotheses (research questions), and rationale for performing the study.

The goal of this proposal is to produce long-term modulation of pain pathways leading to a suppression of pain symptoms in Gulf War Illness patients with pain symptoms by delivery of 10 daily sessions (1 session a day, 5 weekdays a week, for a 2 week period) of transcranial Direct Current Stimulation (tDCS) over specific nerves at the back of the head (i.e. the occipital nerve field (C2)). After identifying Gulf War illness patients with pain symptoms using standard measures, we will address the following specific aims:

Aim 1. Produce long-term modulation of pain pathways reflected in a suppression of pain symptoms by administering repeated sessions of real tDCS targeting the greater occipital nerve at the back of the head.

Hypothesis #1: pain symptoms detectable in measures of pain symptoms (e.g. Visual Analogue Scale and other pain scales) will be improved after repeated sessions of real tDCS when compared to sham tDCS.

Aim 2. Produce long-term modulation of pain pathways reflected in resting state Electroecephalography (EEG) after administering repeated sessions of real tDCS targeting the greater occipital nerve at the back of the head.

Hypothesis # 2: EEG resting state activity changes in both the ascending pathways and descending pathway correlate with suppression of pain. A decrease in activity in the pregenual Anterior Cingulate Cortex (ACC), dorsal Anterior Cingulate Cortex (dACC), insula, and somatosensory cortex after the procedure will be less strongly correlated with pain in comparison to the baseline measurement.

**Describe previous studies that form the basis for the proposed research:**

Gulf War Illness is a chronic and multisymptomatic disorder affecting returning military veterans of the 1990-1991 Gulf war. Pain is a major complaint of Gulf War Illness patients and is a leading cause of disability in veterans diagnosed with musculoskeletal ailments including joint and muscle pain, muscle fatigue, difficulty with lifting objects, and extremity paresthesia's. As a result, the target of the present proposal is the treatment of the pain symptoms, as this is detectable across all Gulf War Illness case classification systems.

Interestingly, Gulf War veterans with pain symptoms often meet the criteria for fibromyalgia, strongly suggesting an overlap in not only pain symptoms but also in the mechanisms of action. Current treatment options for Gulf War Illness are as diverse as their outcomes. Both pharmacological and non-pharmacological modalities are currently used, but only a small subset of patients benefit and most of the patients remain noncompliant to treatment. As current treatment options generate only moderate improvement, modification of cortical physiology by non-invasive brain stimulation would be a valuable and novel therapeutic approach. Our group has developed a new treatment option using transcranial Direct Current Stimulation (tDCS) for the management of pain in patients with Fibromyalgia (Plazier et al., 2014; Plazier et al., 2015). We demonstrated in a recent study published in Neuromodulation (N = 10) and a follow-up clinical trial published in Brain Stimulation (N = 45) that direct stimulation of some nerves at the back of the head (i.e. the occipital nerve field) of fibromyalgia patients seems to cause an overall beneficial effect on general bodily pain (e.g. bone and joint pain) symptoms and confirmed additional improvement on participants' tender points, quality of life, fatigue, and sleep quality (Plazier et al., 2014; Plazier et al., 2015). This effect was maintained within a six-month follow up period. Seventy-six percent of the patients were satisfied or very satisfied with their treatment and 56% of the patients were able to return to work. We further showed that transcranial direct current stimulation (tDCS) can be used to non-invasively modulate these nerves at the back of the head (i.e. occipital nerve field), producing similar results (Vanneste et al., 2011). Our study showed that stimulation of these nerves at the back of the head (i.e. occipital nerve field) using tDCS over 10 sessions decreased bone and joint pain symptoms by 30% in comparison to baseline and 22% in comparison to sham stimulation in patients diagnosed with fibromyalgia (see figure 4, middle)(Plazier et al. 2015c). These findings are further confirmed by our recent pilot study (N = 15) performing 10 sessions of tDCS targeting the nerves at the back of the head (i.e. occipital nerve field), showing pain suppression of 21% and fatigue suppression of 25% for more than 6 months. In another study by our group, we also showed that this stimulation set up has a direct impact on the latencies of the Laser Evoked Potential (Plazier et al., 2015) and confirmed its impact on joint/muscle pain symptoms in patients with fibromyalgia.

Given the promising results for pain symptoms in fibromyalgia patients, we aim to explore this treatment option for Gulf War illness patients with pain symptoms

**What information do you expect to obtain and how will the obtained knowledge be applied:**

To investigate the effects of repeated sessions of tDCS targeting the occipital nerve field on pain symptoms and on global and specific symptoms in GWI participants, we will measure possible changes in symptoms (using questionnaires) and electrophysiological brain activity (resting-state EEG) in a group that receives active tDCS and a group that receives sham tDCS.

The primary outcome measure for pain symptoms will be measured by the Visual Analogue Scale (VAS).

VAS. The Visual Analogue Scale consists of a straight line of 10 cm with the endpoints defining extreme limits such as 'no pain at all' and 'pain as bad as it could be'. The patient is asked to mark his widespread muscle pain level on the line between the two endpoints. The distance between 'no pain at all' and the mark then defines the subject's pain. VAS will be assessed for pain severity. It has been used to measure symptom relief and treatment satisfaction. Several studies have demonstrated that the VAS is sensitive to treatment effects (Haefeli & Elfering, 2006). The VAS has been found to correlate positively with other self-reporting measures of pain intensity. In addition, the difference in pain intensity measured at two different points of time by VAS represents the real difference in magnitude of pain which seems to be the major advantage of this tool compared to others. This will be performed both during Phase I as well as during Phase II after 4-weeks, 12-weeks, and 24-weeks of treatment.

The secondary outcome measures will include measures of of global change as well as changes in specific symptoms of interest related to the Center for Disease Control (CDC) clusters, as GWI is a complex disease with multiple symptom manifestations: Cluster A by the Modified Fatigue Impact Scale (MFIS) and the Pittsburgh Sleep Quality Index (PSQI); Cluster B, mood and cognition, will be assessed by Beck Depression Inventory (BDI); and Cluster C by the Pain Catastrophizing Scale (PCS), McGill Pain Questionnaire (MGPQ), and Pain Vigilance and Awareness Questionnaire (PVAQ).

MFIS. The MFIS is designed to rate the extent to which fatigue affects perceived function (Fisk et al. 1994). The MFIS has a Cronbach's alpha of .80. The Fatigue Impact Scale was sensitive in discriminating the effects of fatigue for patients with chronic fatigue syndrome and essential hypertension.

PSQI. The PSQI is a 19-item questionnaire which assesses sleep quality (Buysse et al. 1989). Internal consistency was adequate for the PSQI (Cronbach's $\alpha = .83$) with a test-retest reliability of .85. Concurrent validity and discriminative validity compared with clinical evaluation, sleep questionnaires, and other questionnaires also support its validity as a measure

BDI. The BDI provides information about depressive feelings and consists of 21 questions (Richter et al. 1998). The BDI test is widely known and has been tested for content, concurrent, and construct validity. High concurrent validity ratings are given between the BDI and other depression instruments as the Minnesota Multiphasic Personality Inventory and the Hamilton Depression Scale; 0.77 correlation rating was calculated when compared with inventory and psychiatric ratings. The BDI has also showed high construct validity with the medical symptoms it measures. Beck's study reported a coefficient alpha rating of .92 for outpatients and .93 for college student samples. The BDI-II positively correlated with the Hamilton Depression Rating Scale, $r = .71$, had a one-week test–retest reliability of $r = .93$ and an internal consistency $\alpha = .91$.

PCS. The PCS indicates the catastrophizing impact of pain experienced by the patient. It consists of 13 statements concerning pain experiences on a 5-point scale (Osman et al. 1997). The PCS has been shown to have an excellent internal consistency: Total PCS = .87-.93, Rumination = .85-.91, Magnification = .66-.75 and Helplessness = .78-.87. The validity of the PCS total and subscales correlated significantly with the Inventory of Negative Thoughts in Response to Pain (INTRP), providing further evidence of concurrent validity for the PCS. Controlling for general psychological disturbance does not substantially change the magnitudes of the correlations between the PCS subscales (.43-.48) or the total PCS and the INTRP.

MGPQ. MGPQ is a self-report questionnaire that allows individuals to give a good description of the quality and intensity of pain that they are experiencing. The internal consistencies calculated included continuous pain, $\alpha = .89$; intermittent pain, $\alpha = .88$; predominantly neuropathic pain, $\alpha = .92$; affective descriptors, $\alpha = .86$; and total score, $\alpha = .91$. The CFA showed that the model fit of the readily interpretable subscales was acceptable, and the goodness of fit index value was .92.

PVAQ. The PVAQ measures the preoccupation with or attention to pain and is associated with pain-related fear and perceived pain severity. It consists of 16 items measured on a 6-point scale (LM. 1997). PVAQ has a high internal

consistency of .89 and was found to correlate highly with related constructs like catastrophizing (PCS) and general body vigilance. The correlation between PVAQ and pain-related fear was moderate, whereas correlations with unrelated constructs like trait anxiety and fear of spiders were low.

Lastly, changes in electrophysiological brain activity will be measured using resting-state EEG.

EEG. Continuous EEG will be recorded from a 64-electrode elastic cap (Neuroscan Quickcap) through a Neuroscan SynAmps2 amplifier using Scan 4.5 software (Compumedics Neuroscan, USA; sampling rate: 1kHz, DC-200Hz). Electrode impedances will typically be below 10 kΩ. The reference electrode will be located on the midline between Cz and CPz and the vertical electroocculogram (VEOG) will be recorded at sites above and below the left eye. Data will be processed off-line using scripts developed in our lab that implement functions from EEGLAB version 11 running under Matlab. Preprocessing will consist of down-sampling to 512 Hz, removing data recorded from poorly functioning electrodes, and correcting for stereotyped artifacts including eye blinks, lateral eye movements, muscle, line noise, and heart rate. Stereotyped artifacts will be identified by visual inspection of the spatial and temporal representation of the independent components. High amplitude, high frequency muscle noise, and other irregular artifacts will be removed. Average Fourier cross-spectral matrices will be computed for frequency bands delta (2-3.5 Hz), theta (4-7.5 Hz), alpha1 (8-10 Hz), alpha2 (10-12Hz), beta1 (13-18 Hz), beta2 (18.5-21 Hz), beta3 (21.5-30 Hz), and gamma (30.5-44 Hz). These frequency bands are based on previous research in tinnitus (Vanneste and De Ridder 2011; Vanneste et al. 2010b, 2011b; Vanneste et al. 2011c). Standardized low-resolution brain electromagnetic tomography (sLORETA; Pascual-Marqui, 2002) will be used to estimate the intracerebral electrical sources. sLORETA computes electric neuronal activity as current density (A/m2) without assuming a predefined number of active sources. The solution space used in this study and associated leadfield matrix are those implemented in the LORETA-Key software. The sLORETA-key anatomical template divides and labels the neocortical (including hippocampus and anterior cingulated cortex) MNI-152 volume in 6,239 voxels of dimension 5 mm3 based on probabilities returned by the Daemon Atlas (Lancaster et al. 2000).

The knowledge gained from this study will provide evidence as to whether or not repeated sessions of real tDCS targeting the greater occipital nerve field is possible in producing long-term modulation of pain pathways reflected in a suppression of pain symptoms and changes in rsEEG.

## STUDY POPULATION

**Number of Participants**

Please indicate the maximum number of participants that will be involved in the research project at UTD affiliated sites:
120

Will participants from non-UTD affiliated site be included?

☐ **Yes** ☒ **No**

If yes, please indicate how many participants are anticipated at each site.

**Characteristics of Participants**

**To which of the following categories do the participants in this research belong?**

| | |
|---|---|
| ☒ Adults | ☐ UTD Students/Staff |
| ☐ Babies and Toddlers (0-3) | ☐ Children in Daycare |
| ☐ Young Children (4-10) | ☐ Children in School |
| ☐ Youth (11-12) | ☐ Teachers or Staff in Schools |
| ☐ Adolescents (13-18) | ☒ Clinic or Hospital Patients |
| ☒ Elderly (>65) | ☐ Clinic or Hospital Staff |
| ☐ Families (Parents w/ Child) | ☐ Institutional residents |
| ☐ Prisoners or parolees | |

| | |
|---|---|
| ☐ Person with language/hearing disability | ☐ Person with emotional disability |
| ☐ Cancer patients | ☐ Non-English speaker |
| ☐ Person with cognitive disability | ☐ Terminally ill |
| ☐ Person with physical disability | |

(If you checked one of the boxes above and are in need of assistance in accommodating a person with disabilities during the research activities, please contact the IRB office.)

| | |
|---|---|
| ☐ Pregnant women | ☐ Women undergoing in vitro fertilization |
| ☐ Fetuses | ☐ Other: |

**Will any vulnerable participants be included?**

Participants can be vulnerable for multiple reasons. Some examples of vulnerable participant include: children, the elderly, pregnant women, fetuses, cognitively impaired individuals, emotionally impaired persons, terminally ill patients, institutional residents, prisoners, parolees, non-English speaking participants, and UTD students/staff.

☐ **Yes** ☒ **No**

If yes, what is the justification for the inclusion of each vulnerable group named?

## Inclusion/Exclusion Criteria

Equitable inclusion of both men and women of all ages, and individuals from diverse racial/ethnic backgrounds, is important to assure that they receive an equal share of the benefits of research and that they do not bear a disproportionate share of its burdens. Participation of adult participants of both genders and diverse racial/ethnic backgrounds should not be restricted without medical or scientific justification.

**Describe the selection criteria and justification for participant inclusion (for instance, if only women are included, explain the rational for excluding men).**

Participants will include male and female US military veterans serving during the 1990-1991 GW and were deployed to the theater of operations in Southwest Asia (i.e., Iraq, Kuwait, and Saudi Arabia) who are capable of understanding and signing an informed consent document.

The subjects will include men and women between the ages of 18 and 50 years old during service in the Gulf War (born between 1940 and 1973). Any race/ethnicity, and both enlisted and officer ranks will be included.

Participants will be recruited, screened and included in the study in an unbiased fashion as regards to race and gender, and efforts will be made to obtain samples of women and minorities (and military ranks) at rates consistent with published estimates of GWI among these groups.

We will include English speakers because not all of the screening forms, questionnaires, and tests are available in languages other than English.

Given the nature of the study only GWI with pain symptoms will be included.

**Describe criteria and justification for any participant exclusion (for instance, if mentally ill participants are to be excluded from the procedure, state why, what steps will be taken to determine mental status).**

We will exclude non-English speakers because not all of the screening forms, questionnaires, and tests are available in any language except English.

Other exclusion criteria are a history of a neurological disorder, including dementia of any type, moderate to severe traumatic brain injury (TBI), brain tumors, present or past drug abuse, stroke, blood vessel abnormalities in the brain, Parkinson's disease, Huntington's disease, or multiple sclerosis. Traumatic brain injury will be screened by history.

No subjects will be enrolled who are cognitively or clinically incompetent to give informed consent.

In addition, the patient cannot be taking medications that interact with the tDCS effect including amphetamines, L-dopa, carbamazepine, sulpiride, pergolide, lorazepam, rivastigmine, dextromethorphan, D-cycloserine, flunarizine, ropinirole,or citalopram. Exclusion criteria also are cardiac pacemakers, implanted medication pumps of any sort, or a history of bad heart disease, a history of seizures and/or family members with a history of seizures, and/or the presence of any metal objects in or near the head which cannot be safely removed for the duration of this study which could be affected by tDCS or affect the administration of tDCS.

**What are the qualifications and training of the staff who will determine inclusion and exclusion?**

Staff will be trained and supervised by Dr. Vanneste before the start of the study. In addition, all personnel involved at the study will have undergone research and ethical training at UTD and have taken and passed DOD required human subject training through CITI.

Dr. Vanneste is Associate Professor in the School of Behavioral and Brain Sciences at UT Dallas. Dr. Vanneste's research focuses on understanding the neural mechanisms underlying disorders (e.g. tinnitus, fibromyalgia, pain) and to develop novel invasive and non-invasive neuromodulation treatments for those who suffer from these disorders. He has also run a large scale clinical trials in human subjects using Vagus Nerve Stimulation.

Dr. Hart is a Johns Hopkins trained neurologist is also a Professor of Behavioral and Brain Sciences with a joint appointment in the departments of Neurology and Psychiatry at The University of Texas Southwestern Medical Center at Dallas. Dr. Hart's work has focused on how the brain stores and retrieves memory and applying these findings to investigate dysfunction in this area in patient populations. He has also run large scale investigations in Herpes Simplex Encephalitis, West Nile Virus encephalitis, Gulf War Illness, and PTSD.

Dr. To is has been designing and conducting (HD) tDCS studies in different research populations for Dr. Vanneste's and Dr. Hart's laboratory in the past 3 years. She has a doctoral degree is in Clinical Psychology and has several years

experience in human subjects research.

Ms. Mohan is a speech pathologist who is now obtaining her Ph.D. in cognitive neuroscience in Dr. Vanneste's laboratory. She is trained to administer EEG and apply different neuromodulation techniques (tDCS, TMS, VNS) and has been working in the lab for almost 2 years. She will be supervised by both Drs. Vanneste and To.

Research staff will be trained to monitor all screening and assessment materials for indications of clinically significant symptomatology (e.g., depression, suicidal ideations) and tDCS safety and adverse effects. Data on possible adverse effects will be monitored and discussed in weekly lab meetings by all staff, including study doctor (Dr. Hart Should clinically significant symptomatology be identified, Dr. Hart will determine whether consultation with the participant is warranted and whether referral for further evaluation and treatment is necessary.

**Selection procedures**

Will participants be fully informed about the selection criteria and the selection procedure?

☒ **Yes** ☐ **No**

If no, please explain:

Will a Control Group be used?

☒ **Yes** ☐ **No**

If yes,

☒ Participants will be informed that they may be a member of a control group.

☐ The individual participants will not be informed that they are part of a control group.

Explain:

## RECRUITMENT OF PARTICIPANTS

The identification and recruitment of participants must be ethically and legally acceptable and free of coercion. Procedures used to recruit participants should be designed to reach diverse populations. For example, vulnerable participants, such as persons in nursing homes or institutions, should not be recruited merely for the sake of convenience.

**Recruitment Methods**

- ☒ Advertisement
- ☐ Verbal scripts for face-to-face meeting
- ☐ Letters to potential participants
- ☐ Other, please explain:
- ☐ Phone solicitations
- ☒ E-Mail
- ☒ Web-Based

**Please describe the recruitment procedures including: 1) how participants will be identified; 2) the steps for recruiting participants; and 3) who will have responsibility for recruitment:**

1) Participants will be identified in the North Texas area with symptoms they attribute to service in the 1990-1991 Persian Gulf War.
2) Drs. Hart and Haley have previously DoD funded projects examining GWI from the 1990-1991 Persian Gulf War (approximately 140 participants), and the participants from these previous studies have elected to remain in contact. These potential participants will be contacted to determine their interest in participating in the current study.
4) Flyers will be handed out and publicly displayed at UT Dallas and UTSW sites.
5) E-mail recruitments will only be sent out to to people who have expressed interest in hearing about research studies in Dr. Hart's laboratory.
6) Study information will be posted on Dr. Vanneste's UT Dallas lab website, using the same content of the flyer.

**Please describe how the timing of the recruitment and consenting process will provide potential participants ample opportunity to consider whether or not to participate in the study:**

When potential participants contact the study personnel, they will describe the nature of the study and obtain contact information from the potential participant. Verbal consent will be obtained to administer a short telephone interview that will discuss the following:

- Answer general questions about the study
- Review of all inclusion/exclusion criteria
- Review the proposed timeline of required activities involved in the study should the prospective participant qualify
- Schedule an appointment to undergo the process of informed consent and additional baseline screening procedures.

The study personnel will only obtain enough information to indicate and will only record whether the participant is possibly eligible to participate.
If it is determined during the initial phone consultation that any prospective participant does not qualify for the study, all information obtained about the participant will be shredded. Only the number of individuals who inquired about the study, as well as the reason they failed to meet the study criteria, will be retained for future reporting.

If potential participant is eligible for the study, they have the choice to schedule for an appointment right away or to contact us back to schedule an appointment to give them more time to consider a possible participation in the study. Once scheduled, we will send an electronic copy of the Consent Form to them. This will allow prospective participants to read and gather any questions about the study at their own pace. Note: Prospective participants will be asked to sign the Consent Form only at the UTDallas main Campus at dr.Vanneste's lab. Written informed consent from the participant will only be obtained after explaining the study and answering any questions. Research staff will ask the potential participant if he/she has any questions and if the participant would like to discuss their continued participation with anyone before making a decision. The staff member will then give the participant privacy and time to review and sign the consent form.

**Please describe the measures that will be taken to minimize the potential for undue influence:**

We will ask the following questions before any participant signs the consent form:

1. Can you tell me the main purpose of the study, and why you are involved?
2. Can you tell me the main components of the study that require your participation?
3. Do you understand that signing this Consent Form does NOT mean that you have been officially included in the study, but rather, inclusion into the study will be determined based on outcomes on additional screening measures?
4. If you decide to not participate in the study at any time, what should you do?
5. If you experience any discomfort or symptoms associated tDCS, what should you do?

## Payment for Participation

**Will participants be paid an incentive for participation in research?**

☒ **Yes** ☐ **No**

If yes, please complete the following (mark all that apply):

- ☐ SONA system credit(s)
- ☐ Cash
- ☐ Gift card
- ☐ Other:

Please note: 1) payment amount; 2) payment schedule; 3) will the incentive be pro-rated based on participant's early withdrawal?

Human subjects will receive a total amount of $250 for completing all visits. After the last treatment session at visit 11 they will receive $100 and at the end of the follow-up phase of the study, they will receive $150.

**Will participants be reimbursed for parking, travel, or other expenses related to participation in the research?**

☐ **Yes** ☒ **No**

If yes, please describe:

## INFORMED CONSENT

In research involving more than minimal risk, when capacity to consent is unclear, the capacity to consent must be determined by a physician, clinical psychologist, or by other qualified professionals. Individuals who lack the capacity to consent may participate in research only if consent is given on their behalf by a legally authorized representative.

**Will you obtain written, signed informed consent from each participant/participant's representative?**

☒ **Yes** ☐ **No**

**Will your study involve the use of any language other than English for Informed Consent forms, data collection instruments, or recruitment materials?**

☐ **Yes** ☒ **No**

If "Yes," after the IRB has notified you of the approval of the English version of your forms, you must then submit the foreign language versions along with an English translation for each.

Specify all foreign languages:

**Who will be authorized to obtain informed consent?** Identify by name and training the individual(s) authorized to describe the research and obtain consent form from participants or their legal representatives.

Sven Vanneste, Ph.D. – Associate Professor in BBS, study PI
Wing Ting To, Ph.D. - research scientist in BBS
Anusha Mohan, M.A. - doctoral student

Please see the descriptions above for the qualifications of Dr. Vanneste, Dr. To, and Ms. Mohan

**Will the participants be informed about which information is recorded and stored?**

☒ **Yes** ☐ **No**

If no, explain:

**Who will provide written informed consent/permission/assent?** (Attach copies of all versions that will be used)

☒ Adult Participants (him/herself)
☐ Legally Authorized Representative
☐ Parents (Permission for Minor)
☐ Children (Assent)

**For studies involving the use of children as research participants, please describe how assent will be obtained in a manner that is sensitive to the developmental stage of the participants:**

/

## Process of Consent

Consider: a) the environment and location where informed consent will be solicited; b) the timing of the process (for instance the stress that may be associated with the situation); c) the involvement of someone other than the investigators to help explain the research; and d) opportunity for the prospective participants or their legal representatives to discuss participation in the research with family, friends, or their advisors before signing the consent form.

**Where will the consent process take place?**

All participants will sign the consent form in a quiet testing room at Dr. Vanneste's lab

**How--and by whom--will it be determined whether the participants or their legally authorized representatives understand the information provided?** This section should clearly document that the investigator has an adequate plan in place to assure existence of an acceptable level of comprehension before consent is documented.

The study personnel who administer the consent form will follow strict lab protocol by asking the aforementioned questions about the study (see above on minimizing undue influence) to each participant before they sign the consent form

## Waiver of Informed Consent Process (complete only if you are requesting a waiver of consent)

**Explain why the use presents no more than minimal risk to the participants?**

**Explain why a waiver of informed consent will not adversely affect the rights and welfare of the participants?**

**Why could the research not practicably be carried out with an informed consent from the participants?**

## METHODS AND PROCEDURES FOR THE COLLECTION OF NEW DATA

**Mark one or more of the following that apply:**

- ☒ Interviews
- ☒ Survey/questionnaire
- ☒ Behavioral observation
- ☒ Standardized assessments
- ☐ Deception

**Describe each activity in which participants will be involved:**
Attach surveys, instruments, interview questions, etc. Describe the frequency and duration of procedures, psychological tests, educational tests, and experiments; including screening, intervention, follow-up etc.

Participant's Review of Inclusion/Exclusion Criteria: Prospective participants will initially review general inclusion and exclusion criteria about the study on the recruiting materials where there is contact information to contact a researcher for more detailed information about the study.

Interested individuals will be screened through a phone screen script. Their continued interest in the study confirms that they have met (via self-report) basic inclusion/exclusion criteria.

Administration of Consent Form: When the Consent form is administered, participants will have already acknowledged that they have met the above criteria and have expressed continued interest in participating in the study. If, at that time, they feel that they do not meet these criteria, or have specific questions about these criteria, they will be asked to inform the research team member administering the consent form. If they again meet these criteria to the best of their knowledge, a second set of study screening procedures will be administered to evaluate whether or not they qualify for the study. All of the remaining screening and study procedures described hereinafter will be administered only if the participant has provided consent to participate (i.e., signed the consent form).

It is an eleven day study with four follow-up sessions: 1 week, 4 weeks, 12 weeks and 24 weeks after the last day of stimulation.

Session 1: Pre-tDCS Assessment (approximately 3 hours)

Assessment: At dr. Vanneste's lab, The following questionnaires/tests will be administered:

1. VAS. The Visual Analogue Scale
2. MFIS. Modified Fatigue Impact Scale
3. PSQI. Pittsburgh Sleep Quality Index
4. BDI. Beck Depression Inventory
5. PCS. Pain Catastrophizing Scale
6. MGPQ. McGill Pain Questionnaire
7. PVAQ. Pain Vigilance and Awareness Questionnaire

In addition, changes in electrophysiological brain activity will be measured using resting-state EEG.

Resting state EEG. The EEG procedure is a non-invasive technique that will record brain electrical activity while the participant sits quietly in a chair for 5 minutes with their eyes are closed. In order to do that, a cap with 64 electrodes will be placed on the scalp. The cap is similar to a loose nylon swim cap. The cap will be placed on the participant's head and then a small amount of a salt water mixture will be added to each electrode from the outside of the cap. The cap placement will take up to 30 minutes. This is a common clinical procedure carried out in neurology.

Session 2-10: tDCS stimulation (approximately 45 minutes)

tDCS Stimulation - Participants will be randomly assigned to two different groups after they have finished assessment: the first group will receive real tDCS targeting the occipital nerve field. This group will receive 20 minutes of stimulation targeting the occipital nerve field area consisting of a current of 1.5mA. The second group (sham, or control, group) receive the same procedure for tDCS but with no delivery of electrical current. For both groups, the stimulation current will gradually ramp up to 1mA during the first 60 seconds of stimulation but the current will only persist for real tDCS group.

Session 11: tDCS stimulation + Immediate Post-tDCS Assessment (approximately 3.5 hours)

tDCS Stimulation - Participants will receive tDCS for 20 minutes (1) at 1.5 mA targeting the occipital nerve field area, or

(2) with no delivery of electrical current (sham, or control, group). For both groups, the stimulation current will gradually ramp up to 1mA during the first 60 seconds of stimulation but the current will only persist for real tDCS group.

Immediate Post-tDCS Assessment - Participants will complete the following assessments that were part of the Pre-tDCS assessment:

1. VAS. The Visual Analogue Scale
2. MFIS. Modified Fatigue Impact Scale
3. PSQI. Pittsburgh Sleep Quality Index
4. BDI. Beck Depression Inventory
5. PCS. Pain Catastrophizing Scale
6. MGPQ. McGill Pain Questionnaire
7. PVAQ. Pain Vigilance and Awareness Questionnaire
8. Resting state EEG.

Sessions 12 (1 week after), 13 (4 weeks after), 14 (12 weeks after) and 15 (24 weeks after) - Post Assessments (approximately 2.5 hours):

Post-assessments will take place at 1 week after, 4 weeks after, 12 weeks after and 24 weeks after the last tDCS session. Follow up-tDCS Assessment are:

1. VAS. The Visual Analogue Scale
2. MFIS. Modified Fatigue Impact Scale
3. PSQI. Pittsburgh Sleep Quality Index
4. BDI. Beck Depression Inventory
5. PCS. Pain Catastrophizing Scale
6. MGPQ. McGill Pain Questionnaire
7. PVAQ. Pain Vigilance and Awareness Questionnaire
8. Resting state EEG.

## METHODS AND PROCEDURES FOR THE USE OF ARCHIVAL DATA

**Will archival data be used?**

☐ **Yes** ☒ **No**

If yes, please continue

**Describe the records: medical, educational, employment existing data set, or pathological specimens:**

**Do you have permission to access the records or specimens?**

☐ Yes, these sources are publicly available. Identify the source (*e.g., database name, website address, etc.*)

☐ Yes, other. Identify the source and describe how you have permissible access to the records.

☐ No

**Number of records or specimens to be used:**

**Will the records you receive be stripped of all identifiers that would make it possible for you to identify a participant?**

☐ **Yes**

☐ **No**

**Describe the identifying information to which you will have access to prior to recording data:**

**Describe the identifying information you will record:**

**Confirm that the data/specimens you wish to review already exist.**

☐ The data set exists

☐ The data set does not already exist

**Confirm that you will not have access to, or create a link, which would make it possible to identify participants.**

☐ I will not have access to, or create a link.

☐ I will have access to a link, explain:

**If this record or specimen became publicly available, could it have negative psychological, physical, economic, sociological or legal consequences for the participant from which it originated?**

☐ **Yes** ☐ **No**

If yes, describe the potential negative consequences.

## RISK/BENEFIT ASSESSMENT

A reasonable person would consider it to be important to know the risk of harm or discomfort when deciding whether to participate in the research project.

### Potential Risks

**Are there risks of physical harm or discomfort associated with the research?**

☒ **Yes** ☐ **No**

If yes, describe: The most common side effect of neurostimulation is temporally local redness of the skin direct under the electrode. This disappears within 1 hour.

- Itching at the site of the electrode, passing within the hour
- Slight feeling of dizziness when starting the stimulation occurs in a small number of patients. This takes only a few seconds and does not affect balance after stimulation
- Very rarely, temporary skin damage may occur under the electrode. This gives a darkening of the skin, which normalizes after a week and heals. The size of such etch is a few millimeters. This is harmless with the current that we will handle, this risk is minimal.

On the safety of transcranial direct current stimulation in healthy volunteers, in 2005 a well-conducted study published in the Journal of Neurology. There is a group of 103 people total transcranial direct current stimulation given to 2 mA. Outside redness and itching they describe a transient slight improvement in language fluency (pronouncing words) or a transient slight delay in language fluency. The technique is considered safe.

**Are there risks of psychological harm or discomfort associated with the research procedure?**

☐ **Yes** ☒ **No**

If yes, describe:

**Are there risks of social harm to the participants associated with the research?**

☐ **Yes** ☒ **No**

If yes, describe:

**Are there economic risks associated with the research?**

☐ **Yes** ☒ **No**

If yes, describe:

**What is your assessment of the overall risk classification of this research?**

☒ Minimal

☐ Greater than Minimal Risk and the study presents the prospect of direct benefit to the participants

☐ Greater than Minimal Risk and the study presents no prospect of direct benefit to the participants, but will likely yield generalizable knowledge about the study question.

### Minimizing Risks

**How will you minimize risks or discomfort?**

☒ Monitor the experiments by professional staff.

☒ Provide opportunities for rest or breaks.

☒ Withdrawal of participant based on specific criteria, explain: All participants who are terminated from the study will have the reason for their termination documented. Reasons for termination may include: lost-to-follow-up, participant-initiated withdrawal, physician-directed withdrawal, completion of study. At the end of the study or if the patient withdraws early, the investigator will discuss follow-up with the participant to ensure the participants receive appropriate ongoing follow-up according to local standard of care.

☒ Remind participant of his/her opportunity to stop or withdraw.

☐ Modification of process, explain:

☐ Other, describe:

**Potential Benefits**

*Benefits to participants do NOT include monetary incentives paid in return for participation.*

**Please describe any direct benefits anticipated for the individual participants in this study:**

There may be no direct benefits to the individual participants in the study. However, they may have short or long-term improvements on their pain symptoms.

**Please describe any potential benefits to society:**

Developing of a new method for the treatment of pain in Gulf War Illness patients.

## DATA PRIVACY & CONFIDENTIALITY

The principal investigator/faculty sponsor is responsible for taking all necessary steps to maintain confidentiality of data. This includes coding data and choosing appropriate and secure ways to store data to prevent unauthorized access to the data.

**Will identifiers or links to an identifier of the participants be stored?**

☒ **Yes** ☐ **No**

If yes, what information that could be linked to the participants will be recorded?

All data collected in this study will be coded. Identifying information, such as name, DOB, physical and contact email addresses and phone numbers, which link a particular participant to their coded data, will be kept in a locked file cabinet in Dr. Vanneste's lab. This information will be stored alongside the signed consent forms. All coded data will be kept in a separate locked file in dr. Vanneste's lab

**Please explain the procedure for de-identifying or anonymizing the data:**

In order to safeguard our participants from a breach in confidentiality, all research data is coded with a unique semi-random subject identifier (URSI). All data after initial entry into the study database is coded based on this participant's number. Dr. Vanneste will have oversight over the stored data. There will not be any personally identifiable information stored in the research database.

**Will you obtain any information containing personally identifying information?**

☒ **Yes** ☐ **No**

If yes, please continue with the following questions.

**If information with personal identifiers will be accessed, will the participants provide consent for storing of personal data or biological specimens in connection with the research?**

☒ **Yes** ☐ **No**

If no, provide justification for a waiver of informed consent:

**Will anyone other than the specified study team, have access to the study records or data? If so, please specify each person's name, role on this study, and affiliation.**

Non-compliance/ unanticipated problems, adverse events, audits and investigation reports will be reported to Human Research Protection Office, USAMRMC Office of Research Protections

**If coded or identified data will be released outside of UTD or its affiliated institutions, please specify the persons/agencies to which the information will be released. Please also indicate the precautions that will be taken to assure that confidentiality will be maintained during transmission of the data.**

De-identified data will be available to Dr. Robert Haley in his role as a subcontract PI at UT Southwestern. Dr. Haley is Professor of Internal Medicine and Director of the Division of Epidemiology in the Internal Medicine Department at UT Southwestern Medical Center and holder of the U.S. Armed Forces Veterans Distinguished Chair for Medical Research Honoring America's Gulf War Veterans. He has conducted extensive research on Gulf War Illness and aid in recruiting, study design, analysis, interpretation of the findings, and manuscript writing.

Coded data might be shared with the Human Research Protection Office, USAMRMC Office of Research Protections, in case of non-compliance/unanticipated probems, adverse events, audits and investigation

**Will your study involve obtaining individually identifiable health information from health care plans, health care clearinghouses, or health care providers?**

☐ **Yes** ☒ **No** ☐ **Not Applicable**

If "Yes," describe the procedures you will use to comply with the HIPAA Privacy Rule:

**Where, how long, and in what format (such as paper, digital or electronic media, video, audio, or photographic) will data be kept? In addition, describe what security provisions will be taken to protect this data (password protection, encryption, etc.).**

All hard-copy clinical and research data, as well as electronic data, collected during this study will be kept in locked file cabinets or on password-protected computers in the laboratory of Dr. Vanneste. Data will be stored indefinitely.

**What will happen to the data after the data analysis is complete?**

☐ Data will be destroyed _____ years after completion of the study

☐ Data will be stored an unspecified length of time

## IRB REVIEW CATEGORY

**THIS SECTION MUST BE COMPLETED**

The DHHS and other Federal Regulations require that the IRB is responsible for determining whether the proposed data collection meets the federal definition of research.

Federal regulations state all activities classified as research must be submitted for IRB review and approval.

Expedited category of review is reserved for research that involves minimal risk and satisfies one or more of following seven categories defined by Federal Regulation (Department of Health and Human Services). All other research involving humans must be reviewed by the FULL BOARD of the IRB.

**Please mark all that apply:**

- ☐ Category 1 - Study of drugs or devices that do not require an IND application, are used consistent w/ label
- ☐ Category 2 - Blood samples by finger/stick or venipuncture from healthy and non-pregnant adults <550ml
- ☐ Category 3 - Prospective biological specimens for research by non-invasive means (ex. hair or nail clippings)
- ☒ Category 4 - Non-invasive procedure used in routine clinical practice
- ☐ Category 5 - Materials collected previously (archival data)
  - ☐ a) for non-research purposes
  - ☐ b) for another research protocol
- ☐ Category 6 - Collection of data from voice, video, digital or other recordings for research purposes.
- ☒ Category 7 - Research on individuals or groups using surveys, interviews, or program evaluation, etc.

## ASSURANCES

**My signature below certifies that:**

I agree to comply fully with the ethical principles and regulation regarding the protection of human subjects in research.

I agree that the information provided in this form and all other supporting documents and forms are accurate and complete.

Copies of all required documentation of consent and any data related to this research are securely stored at:

UTD Building BSB Office Number _____

Sven Vanneste Digitally signed by Sven Vanneste Date: 2017.06.20 10:06:57 -05'00' 6/20/2017

Principal Investigator's Signature Date

_____ _____

☐ Co-Principal Investigator ☐ Faculty Sponsor Date

# Student Conflict of Interest Disclosure for Non-Exempt IRB Application

**Office of Research Compliance**

The purpose of this form is to assist UTD undergraduate and graduate students conducting human subjects research that requires approval by the UTD Institutional Review Board to comply with the terms of UT System Policy 175. Please contact Conor Wakeman (conor.wakeman@utdallas.edu, 972-883-4718) if you have any questions about this form.

| **STUDENT INFORMATION** | |
|---|---|
| Name: | Program: |

UTD Research Conflict of Interest Policy requires annual conflict of interest disclosures from all individuals who contribute significantly to research conducted at UTD. As an investigator on a human subjects research protocol, you are required to disclose the following interests **related to your research at UTD** that may constitute a significant outside interest:

1) Compensation, travel reimbursement or royalty income that exceeds $5,000 in the previous 12 months.
2) An equity interest that represents more than $5,000 in fair market value, more than 10% voting or participating interest, a controlling interest, or any interest (>0%) in a privately held business entity.
3) A gift that represents more than $250 in value (excluding gifts from family members).
4) A fiduciary interest in a business or non-profit entity.

| | **Yes** | **No** |
|---|---|---|
| Do you have a significant outside interest related to your research at UTD that you need to disclose? | | |
| *If yes, you will be provided instructions by the Conflict of Interest Manager to complete a full disclosure.* | | |

**Certification**

In submitting this form, I certify that the above information is true to the best of my knowledge and that I have read and understand the policy on Research Conflict of Interest. I also certify that I will comply with conditions or restrictions imposed by UTD to manage, reduce or eliminate actual or potential conflicts of interest. Furthermore, I supply this information for confidential review by the University and I do not authorize release of it for any other use.

_____ _____

Signature Date

**For Internal Use Only** - Office of Research Review

_____ _____

Sanaz Okhovat Date

Assistant Vice President, Office of Research Compliance

Rafael Martin

Associate Vice President for Research

☐ No Conflict ☐ Full Disclosure Required