PROTOCOL TITLE:

Investigate the anti-pain effect of taVNS in patients with chronic post-stroke upper extremity pain

PRINCIPAL INVESTIGATOR:

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1.0 Objectives / Specific Aims

In this study, our main goal is to establish transcutaneous auricular vagus nerve stimulation (taVNS) as an effective non-invasive neuromodulation method for analgesia of post-stroke upper extremity pain.

We will recruit up to 20 participants with chronic post-stroke upper extremity pain from the greater Charleston area using MUSC COBRE resources. Participants are required to have an ischemic or hemorrhagic stroke that occurred at least 6 months prior and are currently suffering upper extremity pain. Each participant will undergo an in-person visit to our lab at MUSC 30 Bee Street. They will first finish the pain questionnaires and have quantitative sensory testing (QST) conducted to determine baseline pain thresholds. Participants will then receive 30 minutes of taVNS (either active or sham). Upon the completion of the stimulation intervention, they will then be tested for another QST and pain questionnaires. All research is being done at MUSC 30 Bee Street Center for Biomedical Imaging.

Aim 1: Test the safety and feasibility of taVNS in participants with chronic post-stroke upper extremity pain.

Over the last 8 years, our group has demonstrated that taVNS is safe and feasible in several different populations in our previous studies. Specifically, we have demonstrated that taVNS is well tolerated and safe for participants with chronic stroke in our previous clinical trial (Badran et al., 2023, Peng et al., 2023). In this study, we will further verify the safety and feasibility of taVNS in the population with chronic post-stroke upper extremity pain.

Aim 2: Investigate whether taVNS can modulate pain in this population compared to sham.

In this single-visit, single-blinded, sham-controlled pilot trial, we will compare changes in post-stroke upper extremity pain scores and pain threshold derived from QST before and after a 30-minute taVNS intervention, as well as between active and sham taVNS. The findings will help us understand whether taVNS can modulate pain in this population.

2.0 Background

Pain is a common symptom after a stroke. Up to 50% of stroke survivors experience pain, including muscle and joint pain such as spasticity and shoulder pain, complex regional pain syndrome, and central post-stroke pain (Naess et al., 2012, Harrison and Field, 2015). Pharmacological approaches are currently the mainstream first-line treatment for poststroke pain; however, many recommended medications such as antidepressants or anticonvulsants have limited effectiveness in reducing severe pain (Kumar et al., 2009, Treister et al., 2017). A considerable proportion of poststroke pain symptoms become treatment resistant, which then necessitates the employment of opioids, also known for a high risk of dependency (Kim, 2014, Scuteri et al., 2020).

Emerging evidence indicated that neurostimulation therapy approaches, such as deep brain stimulation (DBS) and vagus nerve stimulation (VNS), could be promising alternatives for the pain treatment of refractory patients and have successfully demonstrated analgesic effects in acute pain, post-surgical pain, and chronic pain disorders (Dang et al., 2019, Bittar et al., 2005, Lempka et al., 2017, Boon et al., 1999, Chakravarthy et al., 2015, Bao et al., 2020). However, these brain stimulation methods are significantly limited due to their costly and invasive nature. Thus, developing non-invasive and affordable neuromodulation methods for the treatment of post-stroke pain will be of great benefit.

Recent innovations in VNS have enabled non-invasive administration at the ear, known as transcutaneous auricular vagus nerve stimulation (taVNS), which has become popular due to minimal side effects and low cost. Importantly, taVNS may produce analgesia and reduce opioid withdrawal by facilitating the release of endogenous opioids via activation of afferent subcortical cranial nerve networks, which subsequently modulate afferent cortical vagal networks controlling pain. However, only limited knowledge currently we have for the feasibility and efficacy of taVNS analgesia in post-stroke pain.

3.0 Intervention to be studied (if applicable)

The intervention we are studying is transcutaneous auricular vagus nerve stimulation (taVNS) which is simply electrical nerve stimulation administered at the ear which targets the auricular branch of the vagus nerve. In this study, taVNS will be administered using the Spark Sparrow Ascent System which is a non-significant risk

investigational device. The Spark Sparrow Ascent System is based on an FDA-cleared device provided by Spark Biomedical and has completed all safety and compliance testing. taVNS is a non-significant risk method that has been approved by the MUSC IRB for many ongoing taVNS trials. Drs. Peng and Badran are the PI or Co-I of more than seven ongoing taVNS trials. The Spark device summary has been uploaded to the MUSC IRB portal.

In this study, we will use the device as an anti-pain device in participants with chronic post-stroke upper extremity pain. Participants will be randomized to receive 30-minute active taVNS (tragus and cymba conchae) or sham taVNS (earlobe) during their in-person visit. In prior studies in our laboratory, we demonstrated that taVNS can be safely and feasibly administered in chronic stroke populations (Peng et al., 2023, Badran et al., 2023).

4.0 Study Endpoints (if applicable)

Primary Outcome: *Safety and Feasibility*

The main outcomes of this pilot trial will be the safety and feasibility of implementing taVNS in the population with chronic post-stroke upper extremity pain.

Secondary Outcomes: *Quantitative Sensory Testing (QST)*

We will systematically determine information about Aβ (sensory), Aδ (pain), and C (pain tolerance) fiber activity with a 30 × 30 mm thermode attached to the non-affected forearm (left arm) of participants (TSA2 thermode; Medoc, Durham, NC, USA). Using the TSA2, we will determine heat sensory, pain, and tolerance thresholds using the method of limits, beginning at 32°C and increasing by 0.5°C per second. Participants will be asked to press a button (to record temperatures) when the stimulus is first detected (sensory threshold), when it becomes painful (pain threshold), and then when the stimulus is intolerable (pain tolerance). When 'intolerable' is indicated, the thermode ceases heating and quickly returns to 32°C. This is repeated for 5 trials to obtain average sensory, pain, and tolerance thresholds. We will acquire QST data before and after the 30-minute taVNS. We will explore the analgesic effects by comparing the pre- and post-intervention QST ratings.

Secondary Outcomes: *Subjective Pain Ratings*

Participants will rate their post-stroke upper extremity pain intensity before and after the taVNS using a standard numeric pain rating scale (0-10). We anticipate participants will rate lower pain intensity post-intervention.

5.0 Inclusion and Exclusion Criteria/ Study Population

Twenty participants with upper extremity post-stroke pain of all ethnic and racial categories will be accepted into this study protocol. No preference will be given based on race, gender, or ethnicity. Pregnant females and children under the age of 18 will be excluded for safety reasons.

Inclusion Criteria:

- Age 18-80
- Have the capacity and ability to provide one's own consent in English and sign the informed consent document.
- Ischemic or hemorrhagic stroke that occurred at least 6 months prior
- Unilateral stroke lesions in the left hemisphere
- Right upper extremity pain

Exclusion Criteria:

- Primary intracerebral hematoma or subarachnoid hemorrhage
- Documented history of dementia

- Documented history of uncontrolled depression or psychiatric disorder
- Uncontrolled hypertension despite treatment, specifically SBP (Systolic Blood Pressure) / DBP (Diastolic Blood Pressure) >=180/100mmHg
- Pregnancy

6.0 Number of Subjects

We will recruit 20 participants with chronic post-stroke upper extremity pain for this study.

7.0 Setting

All participants will complete the study tasks in our experimental room at the MUSC 30 Bee Street Center for Biomedical Imaging. Subjects will be consented and educated about the study, and complete the rest of the study procedures.

8.0 Recruitment Methods

This study will recruit from the Registry for Stroke Recovery (RESTORE-Pro#00037803, IRB approved 9/6/14) which is a research tool sponsored by the National Institutes of Health (NIH) Center of Biomedical Research Excellence (COBRE) in Stroke Recovery with subjects consented for future contact to support stroke recovery research conducted at MUSC. RESTORE staff will query the registry for potential subjects and provide the Principal Investigator (PI) with the contact information of subjects who meet their criteria. The PI or research staff will then contact subjects to confirm whether they are interested in the study following the cold call recruitment script. Additionally, RESTORE staff can also give rack cards to interested RESTORE (stroke registry) individuals. They will be further screened for potential enrollment.

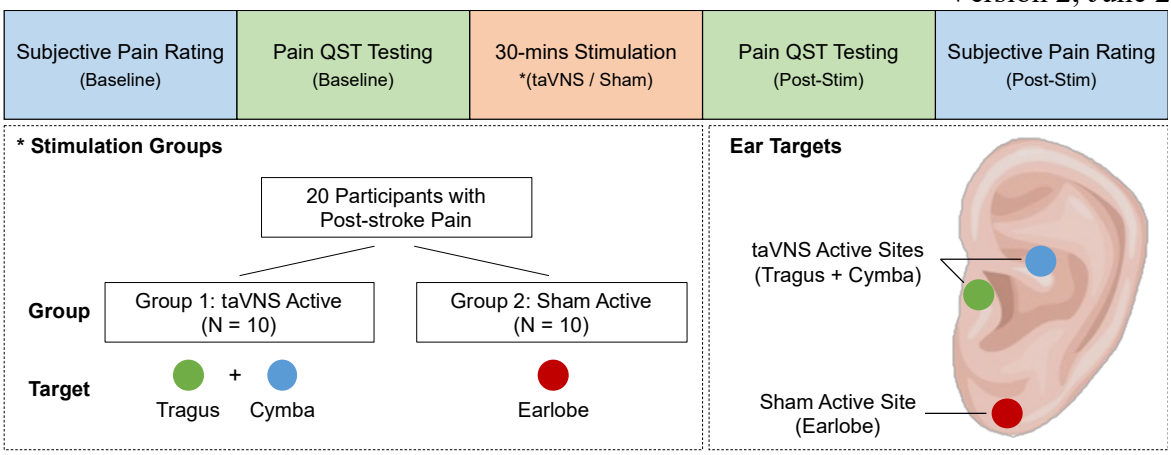
9.0 Consent Process

Consent procedures will be conducted in a private, quiet room at the MUSC 30 Bee Street Center for Biomedical Imaging. Approved study personnel will walk through the consent procedures with the participants. Furthermore, after the consenting procedures, the consent form will be printed and provided to all participants to independently review to ensure understanding, including describing the laboratory measures, study duration, and equipment and materials. The study team will describe confidentiality/privacy measures, participant right to withdraw, risks/benefits. In addition, participants will be prompted to ask questions throughout consenting to further ensure understanding. After signing the consent form, they will also be offered a hard copy.

10.0 Study Design / Methods

Study Overview:

After determining eligibility and interest, written informed consent will be obtained from participants at the MUSC Center for Biomedical Imaging. After consent is obtained, the participants will then complete a pregnancy test and conduct a brief daily life functioning battery. Enrolled participants will start the experiment. They will first finish the subjective pain rating and have quantitative sensory testing (QST) conducted to determine baseline pain thresholds. Participants will then receive 30 minutes of taVNS (either active or sham). Upon the completion of the stimulation intervention, they will then be tested for another subjective pain rating and QST. The timeline of the experiment and group assignment overview are displayed below.



Experiment Overview – Investigate the anti-pain effect of taVNS in chronic post-stroke upper extremity pain

Recruitment, Screening, and Consent Procedures:

Recruitment will be conducted by the study team utilizing the MUSC RESTORE list to identify and contact prospective chronic stroke patients. Participants who are found to be appropriate candidates will be offered to be phone screened and educated regarding the study's details. If interested in participating in the study, they will be consented and enrolled into the study's protocol. Additionally, RESTORE staff can also give rack cards to interested RESTORE (stroke registry) individuals. If interested in participating in the study, they will be consented and enrolled into the study's protocol.

Daily Life Function Battery:

All participants will complete a daily life function battery after being enrolled. This battery includes the following questionnaires in specific life domains that will be used to identify baseline characteristics of individuals: Demographics; Pain Screening; Substance Use: TAPS; Pain Intensity & Interference: PEG; Physical Functioning/QDL: PROMIS Physical Functioning 6b; Sleep: PROMIS Sleep Disturbance 6a; Sleep: Sleep Duration; Depression: PHQ9; Anxiety: GAD7.

Pregnancy Test Procedures:

If participants are a person of childbearing age, they will be provided with a pregnancy test strip After completing the pregnancy test, participants with negative results will be asked to continue to the remaining study procedures, whereas those with a positive result will be debriefed and released.

Subjective Pain Rating:

Participants will rate their post-stroke upper extremity pain intensity before and after the taVNS using a standard numeric pain rating scale (0-10).

Quantitative Sensory Testing Procedures:

We will measure pain assessments by administering cutaneous stimuli via the Medoc Pathway System (Medoc, Durham, NC) using a 30 x 30 mm ATS thermode. QST will be done using method of limits testing on the thenar eminence of the non-affective forearm (left arm). A program will be set up to administer 5 hot stimuli with random durations between each trial. The ATS thermode begins at 32 deg C and increases by 0.5 deg C per second. Participants will be asked to press a button in order to signify three different measures: (1) sensory threshold, or the temperature at which the stimulus becomes noticeable, (2) pain threshold, or the temperature at which the stimulus becomes painful, and (3) pain tolerance, or the temperature at which the stimulus becomes too painful to tolerate. Measuring these thresholds will yield information about Aβ, Aδ, and C fibers, respectively. The device will be set to stop heating at 51.5º C and stop cooling at 0º C to avoid tissue damage. The QST procedures will be tested before and after the taVNS.

taVNS Procedures:

All stimulation will be conducted using the Sparrow Ascent transcutaneous auricular neuromodulation (tAN) device manufactured by Spark Biomedical (Dallas, TX). These tAN devices are portable, wearable systems that have 2

channels of stimulation (auricular vagus, auricular trigeminal, and both). Two individual stimulation frequencies will be set: 15 Hz at cymba concha and 100 Hz adjacently anterior to tragus. The pulse duration will be set to 250 μs for all participants. The stimulation intensities delivered (in mA) will be a standardized 2X Perceptual Threshold. This means that all individuals will first have a perceptual threshold conducted, during which incremental increases and decreases in current intensity will be applied until the participant barely feels the stimulation. That is considered the perceptual threshold. All stimulation then will be delivered at 2X this value. Perceptual threshold will be conducted at the beginning of the taVNS intervention. This is how we have conducted stimulation at MUSC in prior IRB-approved studies which have been safe and rated comfortable and not painful. Sham stimulation will be administered at identical parameters of cymba concha, however, the electrodes will be attached to the earlobe, which is not believed to have a high density of cranial nerve innervation. If the participant states that the stimulation intensity is discomforting or imperceivable in any of the stimulation groups, the researcher will gradually decrease until a comfortable stimulation intensity is achieved. The taVNS session will last for 30 minutes.

12.0 Data Management

All data will be stored in the Redcap database as well as in paper documentation. Information about the participants (including their identifiable private information) may have all their identifiers removed and used for future research studies or distributed to other researchers for future research without additional informed consent. After participation, RedCAP data will be downloaded in Excel format to the secure MUSC server. Paper documentation will be stored in locked cabinet within a locked office of the study team. In terms of publication, data will be published in aggregate form, so individual participants will not be identifiable in the final manuscript. No identifying information will be published.

Confidentiality and Quality Control: All study personnel will complete Social-Behavioral-Educational research CITI training, and also complete in-lab training regarding data security practices. Study personnel will be trained in the IRB protocol. The investigator, and co-investigators will be available to monitor data collection to ensure quality, confidentiality, and adherence to the IRB protocol.

All study's procedures will take place at the MUSC 30 Bee Street Neuroimaging Center. Regarding documentation, participant names will appear only on the IRB-approved Consent and HIPAA.

The RESTORE registry (Pro#00037803), from which this study will recruit subjects, also serves as a data analysis tool by which interdisciplinary teams may share data across projects and provide MUSC's stroke recovery research community with a more complete registry with key stroke elements. Some subjects may have participated or will participate in other stroke related research studies at MUSC. Sharing data from this and other stroke research studies with RESTORE will allow for more targeted recruitment efforts in the future and could reduce the burden placed on subjects by reducing the duplicative efforts of collecting common data and physical function assessments requested by multiple studies and storing them in one centralized and secure location. The third Aim of this study leverages this ability, as other studies will be better able to target their recruitment based on the information collected in these assessments. De-identified information/data will only be shared once study is completed.

13.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

There are three areas in which safeguards to protect subjects from undue risk require discussion. These include: 1) procedures used to obtain informed consent, 2) procedures used to ensure confidentiality of the subject data, and 3) procedures used to minimize possible risks associated with the laboratory procedures. Regarding informed consent, participants are fully advised on the research procedures to be used, the amount of time required of them, the possible risks and benefits of the procedures, their right to refuse participation in the study without prejudice, their right to terminate participation at any moment without prejudice, and the name and telephone number of the principal investigator. All subjects will be required to have the capacity to consent. Regarding confidentiality, subjects are informed that the information they provide will be kept strictly confidential, with access limited to the research staff. Participation in the study will be treated as confidential, as will all records. The identity of subjects will be protected with alphanumeric codes. All data will be kept in locked file cabinets or on secure servers designed for use and access by the study team only.

We do not anticipate any adverse events to occur in this study, however, the experienced research team has a long-standing record of recording and reporting unanticipated adverse events to the IRB. We will report any adverse event within 48 hours to the IRB.

14.0 Withdrawal of Subjects

Participants will be informed during consenting that they are free to withdraw from the study at any time. They will be informed that they are not obligated to participate once the study is initiated and in particular will be reminded prior to taVNS/VNS stimulation they may discontinue stimulation and/or the experiment at any point. taVNS has been a very safe procedure and we do not anticipate subject withdrawal due to taVNS side effects. No participants in previous studies utilizing taVNS have been forced to withdraw for medical or physiological purposes, and we do not anticipate any issues during this study. If participants begin to experience ear pain, an attempt can be made on the other ear, as well as a reduction in the intensity of stimulation before termination would be required. We will be monitoring the stimulation session and if a patient is extremely sensitive to the device we might consider terminating. In that case, the participant and their guardian would be informed of the need for termination.

15.0 Risks to Subjects

Ear Stimulation:

Ear stimulation is safe, however, there are some risks associated with stimulating the ear: There may be local discomfort. This will likely be temporary. In extreme cases, burns might occur. We will monitor any potential burns via direct communication with participants and will stop stimulation and advise subjects to apply vitamin E cream. The tissue surrounding the ear may be sensitive, sore, or feel slight numbness. Hopefully, this will be temporary and will go away after the stimulation is turned off.

Safety in Case of Pregnancy:

This protocol will exclude pregnant women. The risks of using taVNS with pregnant women are currently unknown. If in the screening and consent a patient is a woman of childbearing age, they will be tested prior to receiving any taVNS.

Potential Headache, Dizziness, and Facial Pain:

Ear stimulation might cause headaches or face pain, which should resolve shortly after treatment.

Potential Decrease in Heart Rate:

Ear stimulation may slow heart rate. In rare cases (less than 1%) decreased blood pressure or fainting may occur. We expect no significant changes in heart rate or blood pressure, or fainting to occur. For the initial sessions, all subjects will be stimulated while they are seated, never standing. We expect no significant changes in heart rate or blood pressure, but if this occurs, the study team will evaluate the situation and either decide that the patient should be dropped from the study, or do all sessions lying on a couch, or with lower doses.

QST Pain Assessments:

The Medoc pain assessment system has been used safely by Co-I Dr. Borckardt and others for over a decade now. The pain is unpleasant but there are limits to the amount of pain, and there have been no adverse events over 5 prior MUSC IRB-approved pain studies using this approach. Some participants may report feeling anxious before experiencing a painful stimulus, however, this is rare and if occurs, the participant will be able to request to stop voluntarily.

Unknown Risks:

There is always the possibility of other risks for a relatively new technology. The Study team will let the participant know if they learn anything that might make the participant change their mind about participating in the study.

Loss of Confidentiality:

There is a risk of a loss of confidentiality of personal information. Subjects are informed that the information they provide, as well as participation in the study, will be kept strictly confidential, with access limited to the research staff. The identity of subjects in databases will be protected with alphanumeric codes. All data will be kept in locked file cabinets or on secure servers designed for use and access by Study Team members only.

16.0 Potential Benefits to Subjects or Others

There will be no direct benefit to the participant in the study. Data from this study, however, will benefit society by improving the understanding of if and how taVNS controls pain and potentially work towards developing a novel therapeutic device.

17.0 Sharing of Results with Subjects

There is no plan to inform subjects of the results of the study, but they can always contact the research staff and ask. If there are significant new findings during the course of the study, they will be notified.

18.0 Drugs or Devices

tAN Device (Spark Biomedical Sparrow Ascent)

tAN has been determined a non-significant risk determination of this device. We are using the Spark Sparrow Ascent tAN system outlined in this document, based on the FDA-cleared Sparrow System (K201873). IRB 1 has consistently given NSR status for all prior taVNS studies at MUSC, including studies in stroke patients (Badran), brain damaged newborns learning to feed (Jenkins, Badran), Parkinson's Disease (Hinson, Badran) and healthy volunteers (Badran, Austelle).

QST Pain Device (Medoc Pathway TSA2)

Medoc's TSA2 offers thermal stimulation in the full range from sensation to pain, in heat and cold, using one or two thermodes simultaneously. A wide variety of thermodes is available for each body site or stimulation profile. Excellent temperature control and fast rates make the device accurate, the test repeatable, and suitable for a great number of applications. Medoc has been developing and manufacturing QST devices in the thermal, pressure, and vibratory modalities for over 30 years. This system has been IRB-approved here at MUSC in prior work conducted by the Co-Is (Badran, Borckardt).

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