PROTOCOL TITLE:

Combining Transcutaneous Auricular Vagus Nerve Stimulation (taVNS) with Transcranial Magnetic Stimulation (TMS) to Enhance Cortical Excitability

PRINCIPAL INVESTIGATOR:

Bashar W. Badran, Ph.D.

1.0 Objectives / Specific Aims

The majority of patients suffering from stroke have functional motor impairments that negatively affect their mobility and daily life activities causing a low overall quality of life(1, 2). The most effective way to reduce these motor deficits is with task-specific rehabilitation training(3-7). Recent studies show that noninvasive brain stimulation can enhance task-specific training(8-10). Specifically, repetitive transcranial magnetic stimulation (rTMS) can noninvasively modulate the primary motor cortex(11-13). 1Hz rTMS has a cortically suppressive effect(14), whereas 10 and 20Hz stimulation paradigms induce cortical excitability(11, 12). Increases in excitability last between 10-60 minutes depending on the form of stimulation. These effects are likely long-term depression (LTD) and long-term potentiation (LTP) like neuroplasticity states, as pharmacological NMDA receptor blockade prevents these TMS-induced changes(15).

rTMS is emerging as a potential rehabilitation tool – when delivered to the motor cortex, rTMS can correct post-stroke interhemispheric-imbalance by either reducing excitability in the contralesional motor cortex with 1Hz rTMS(16) or increasing excitability in the ipsilesional motor cortex using 10 and 20Hz rTMS(17, 18). Findings from these studies suggest that rTMS may develop into a promising adjuvant to conventional motor rehabilitation, however a recent large-scale trial was negative however, showing that more work is needed to understand how best to use rTMS for stroke motor recovery.

Can we enhance the effects of rTMS on motor cortex? A different brain stimulation modality, cervically implanted vagus nerve stimulation (cVNS) can enhance neuroplasticity and facilitate rehabilitation, especially when paired with an intervention such as task-specific training(19, 20). There is a new noninvasive form of this method, transcutaneous auricular vagus nerve stimulation (taVNS). This may also facilitate plasticity and is being investigated in the enhancement of motor learning and recovery in a specific paired fashion. The timing of the paired VNS is critical to the desired neuroplastic changes(21-23), as the behavioral effects of paired therapy disappear when behavior is not intricately synchronized with stimulation. Could pairing taVNS with TMS boost the effects of TMS on cortex, and potentially emerge as a stroke recovery tool? As a first step in this direction, we propose a basic, mechanistic pilot study exploring the use of paired taVNS/TMS to further enhance motor cortex excitability in 24 healthy individuals in a 4 visit, randomized, sham controlled, counterbalanced study.

Aim 1. Determine the effects of taVNS on motor cortex excitability. We hypothesize that taVNS alone (sham rTMS + active taVNS) will induce increases in motor cortex excitability (post-stimulation compared to baseline). We believe these changes will be of a lesser magnitude than those of TMS alone (active rTMS + sham taVNS) due to the indirect mechanistic approach of taVNS.

Aim 2. Determine whether taVNS-paired TMS is more effective at inducing cortical excitability than TMS alone. We hypothesize that pairing two forms of neuromodulation (active rTMS + active taVNS) will increase TMS-induced cortical excitability in the motor cortex when compared to single modality approaches (active rTMS + sham taVNS; sham rTMS + active taVNS). Furthermore, we believe this increase is timing sensitive, and the paired approach will induce larger TMS-induced cortical excitability compared to unpaired neuromodulation (active taVNS + active taVNS).

2.0 Background

85% of stroke cases result in reductions in motor function, and this has a severe negative impact on daily living(1, 2). Motor rehabilitation training paradigms, such as task-specific training are common interventions to restore function in the affected limbs(3-7). Neuromodulation techniques such as transcranial magnetic stimulation (rTMS) are becoming a widely used tool to augment motor training. rTMS is most commonly used to modulate cortical excitability in the motor cortex of individuals receiving motor rehabilitation training (17, 18) and is also used to treat a variety of non-motor stroke symptoms such as depression(24). rTMS is a promising tool for neurorehabilitation, however its cortical effects are transient and behavioral benefits aren't seen for several weeks. There is a need for noninvasive

neuromodulatory techniques that can induce robust changes in cortical excitability to facilitate motor recovery after stroke and enhance and accelerate the neuroplastic changes induced by rTMS alone.

Dr. Badran (PI) and the team at the MUSC Brain Stimulation Lab have pioneered a noninvasive form of vagus nerve stimulation (VNS) known as transcutaneous auricular vagus nerve stimulation (taVNS). Our group demonstrated taVNS activates the afferent vagal system by using cardiac effects as a reliable biomarker to determine optimal stimulation parameters. Following the optimization of the parameter space, Dr. Badran conducted a novel concurrent taVNS/fMRI study exploring the direct brain effects of taVNS which revealed activation of the vagal afferent network induced by stimulation of the ABVN(25). This taVNS system can rapidly translate the promising basic animal studies revealing the neuroplasticity effects of paired-VNS, and a small open-label trial of paired taVNS is planned at MUSC later this year.

The research team is poised to develop a unique, novel, multimodal form of brain stimulation – combining both taVNS and TMS in a time dependent, synchronized manner. We plan to develop this taVNS/TMS system as Aim 1 of this proposal. Critical to understanding the faciliatory effects of pairing taVNS with TMS is the underlying principle of timing the paired stimulus which be better understood. Aim 2 explores the timing effects of paired taVNS/TMS in a classic MEP paradigm, which can help elucidate whether paring of stimulation is critical to the excitability changes. This proposal aims to create a concurrent taVNS/TMS system that can administer both paired- and unpaired- taVNS/TMS stimulation to the motor cortex and facilitate cortical excitability. We will subsequently use this system to investigate whether the timing of taVNS is critical to inducing motor cortex excitability.

rTMS-induced increases in cortical excitability improve functional outcomes post-stroke

Repetitive transcranial magnetic stimulation (rTMS) is a safe, noninvasive form of cortical brain stimulation that transiently induces neurophysiologic changes. When delivered at sub-threshold intensity to the motor cortex has been used to correct post-stroke interhemispheric-imbalance by either reducing excitability in the contralesional motor cortex or increasing excitability in the ipsilesional motor cortex. (17, 18).

Studies have demonstrated that single sessions of high frequency stimulation (20Hz) of the motor cortex elicits transient increases in MEP size. This modulation of cortical excitability makes rTMS an exciting tool for motor rehabilitation, as motor cortex excitability is involved in the learning of motor skills (26, 27). rTMS is a safe method of inducing motor cortex excitability and is in neurorehabilitation to either inhibit contralesional motor cortex or excite ipsilesional motor cortex in order to restore interhemispheric competition post-stroke.

Transcutaneous Auricular Vagus Nerve Stimulation (taVNS) may facilitate neuroplasticity:

Cervically implanted vagus nerve stimulation (cVNS) is an invasive form of neuromodulation which has been demonstrated to induce broad downstream neuroplastic cellular effects. These effects are driven by the locus coeruleus (LC) which serves as the main entry of the vagus nerve into the central nervous system. Lesions to LC inhibit this noradrenergic-driven neuroplasticity(28, 29). VNS is an influencer of neural plasticity when paired with specific behavior (30-33).

The auricular branch of the vagus nerve (ABVN) is the target of a novel form of noninvasive vagus nerve stimulation known as transcutaneous auricular vagus nerve stimulation (taVNS)(11)(14, 16, 29-34). Dr. Badran (PI) and the team at the MUSC Brain Stimulation Lab have pioneered several of the early studies demonstrating the biological effects of taVNS. As a cost-effective, noninvasive alterative to implantable cVNS we believe taVNS can mimic the effects of cVNS and be easily combined to enhance neuroplasticity.

Pairing taVNS with TMS might synergistically increase the effects of TMS alone

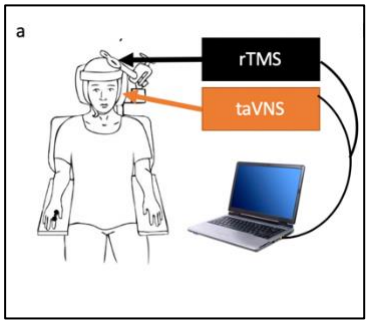
Rat models of VNS-paired therapy have demonstrated that timing is critical to the neuroplastic effects of VNS. Rehabilitation training without VNS takes a long time, and VNS alone fails to restore the behavior without the paired training. Delivering VNS immediately following training fails to enhance the training. Therefore, it is important to synchronize stimulation precisely with the paired training.

Aim 1 of this proposal establishes a computerized system that can synchronize two forms of neuromodulation – TMS and taVNS. Using this system, we will investigate whether the timing of taVNS impacts the cortical excitability effects of TMS alone.

3.0 Intervention to be studied

We will be using a combined taVNS/TMS system that will deliver taVNS with TMS training in a healthy population. The rational and overview is described below:

Pairing taVNS with TMS



Aim 1 of this study will establish a computerized system that facilitates the intricately timed paring of TMS and taVNS in healthy individuals. High frequency rTMS is a safe form of neuromodulation that is FDA-approved for depression and OCD. High-frequency TMS delivered to the motor cortex has been demonstrated to facilitate cortical plasticity.

taVNS is a safe form of cranial nerve stimulation that has been developed at MUSC by the PI of this project and is actively being used in several MUSC clinical trials exploring its use as a potential treatment for neuropsychiatric disorders. taVNS is also an enhancer of neuroplasticity.

This study will combine two safe, validated forms of neuromodulation delivered either concurrently (paired) or independently (unpaired).

Motor-Evoked Potentials.

MEP Recordings. EMG recordings using Ag/Ag Chloride electrodes will be placed on the subject's hand muscle in order to record motor excitability. The EMG recording electrodes will be connected to a standard CED (Cambridge Electronics Device) amplifier and pre-amplifier. Spike2 software will be used to analyze and record the MEPs. The level of stimulation required to produce a MEP of 1mV will be determined prior to collecting baseline MEPs. Baseline MEPs will be collected at the pre-determined stimulation output for 1mV. Another series of pulses will be analyzed in comparison with the first. If the average amplitude is within 25%, we will proceed with experiment. If not, another series of baseline pulses will be obtained repeating the above process, up to 4 times. If the baseline remains highly variable, the participant will be withdrawn. Following rTMS stimulation, the same pattern of single pulses will be recorded at 0, 10, 20, 30..

The key assumption that underlies the use of MEP measurements as a "read-out" of upstream processes influencing the motor system is that the amplitude of MEPs recorded (via EMG) from peripheral muscles is a product of top-down influences on M1 (such as attention/volitional control), combined with changes in excitatory/inhibitory pre-synaptic (inter)neuronal balance (i.e. due to rTMS at the stimulation site), and the post-synaptic excitability of corticospinal output projections (Bestmann and Krakauer, 2015). This method has been well-established as safe and reliable in the field of TMS research and in the brain stimulation laboratory.

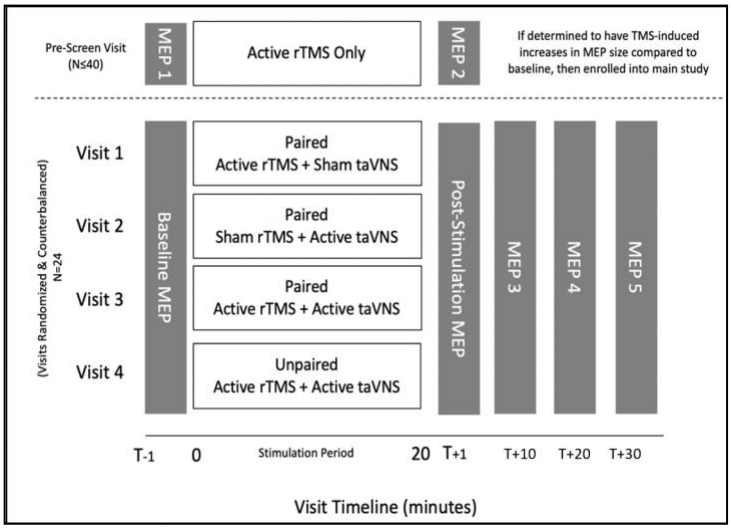
Neuronavigation. Brainsight Neuronavigation equipment and software will be used (https://www.rogue-research.com/tms/brainsight-tms/) to help ensure that the stimulation site remains unchanged during and between recordings and thereby decrease MEP variability.

4.0 Study Endpoints

This figure describes the data collected and the endpoints that will be utilized. The endpoints revolve around motor physiology outcomes (Motor Evoked Potentials - MEPs) at baseline as well as at 10-minute increments post-stimulation

The MEP recordings will be used to track motor excitability outcomes.

More details about endpoints are described in the study design section.



5.0 Inclusion and Exclusion Criteria/ Study Population

Inclusion Criteria: Age 18-80, endorsing good health with no history of mental or physical illness or implanted metal in their body above the level of the neck.

Exclusion Criteria: Participants will be excluded for the following: no TMS-induced motor cortex excitability changes in response to 20Hz motor cortex rTMS, any recent psychiatric or physical illness; history of CNS disease, concussion, overnight hospitalization, or other neurologic sequelae, tumors, seizures, frequent or severe headaches; any psychotropic medication taken within 5 half-lives of procedure time; abuse or dependence of drugs (excluding nicotine and caffeine), currently taking medications that lower the seizure threshold; taking any of the stimulants, thyroid medication, or steroids; implanted devices/ferrous metal of any kind; history of seizure or seizure disorder; or inability to determine motor threshold, and TMS resting motor thresholds over 65% of total machine output assessed on experimental visit 1. Pregnant females and children under the age of 18 will be excluded for safety reasons. No vulnerable populations or special classes of subjects will be considered for participation.

6.0 Number of Subjects

Total Planned Enrollment: up to 40 healthy individuals

Healthy individuals of all ethnic and racial categories will be accepted into this study protocol. No preference will be given based on race, gender or ethnicity.

7.0 Setting

This study will be conducted at the MUSC Brain Stimulation Lab in the MUSC Institute of Psychiatry. The PI of this study has an office on the floor and is directly accessible to medical and professional staff for the safety of participants.

8.0 Recruitment Methods

Recruitment will be conducted using IRB-approved e-mail blasts (to students and staff), and word of mouth.

9.0 Consent Process

Written informed consent will be obtained from the participant by the PI or designated study team personnel. Consent process will occur at the MUSC Brain Stimulation Lab. Only individuals who pass an initial phone eligibility screening will be eligible to consent in person. This consent will happen on or before visit 1.

10.0 Study Design / Methods

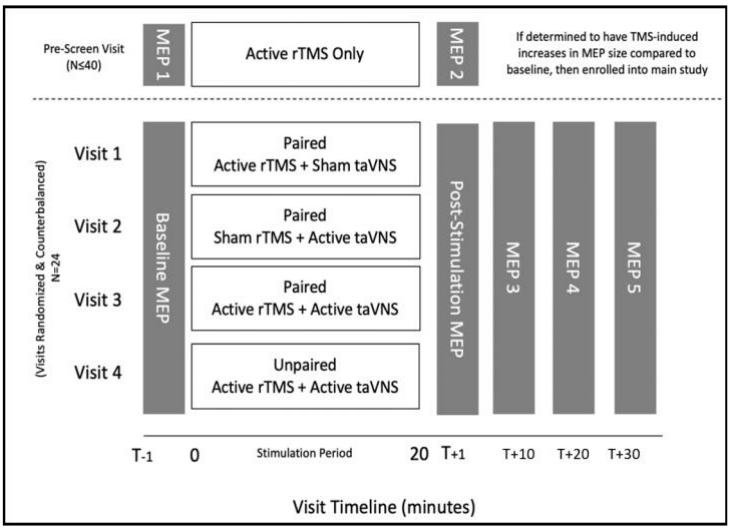
Screening

Up to 40 participants will be screened for inclusion/exclusion criteria, and if enrolled, will attend up to 5 visits at the MUSC brain stimulation laboratory. Participants will sign consent before visit 1, including a urine pregnancy screen (if female). We expect this study to be completed over the span of 6-8 months.

Participants will be screened for taVNS and TMS contraindications before enrolling in the study and written informed consent will be obtained from all participants prior to participation in the experimental paradigm.

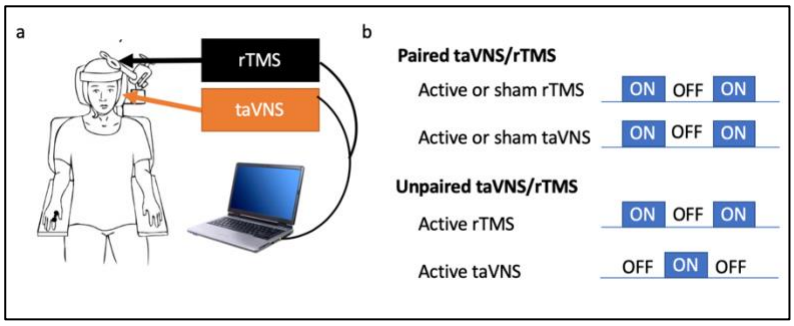
For more information on taVNS and TMS screening please see the uploaded taVNS screening form.

Study Design



We will enroll 40 healthy individuals into a motor excitability prescreening visit (20Hz rTMS to motor cortex flanked by pre- and post-MEP), and from this prescreen cohort subsequently enroll a total of 24 healthy participants (of whom had increases in motor excitability in the prescreen) into a 4 visit, randomized, sham-controlled trial exploring various forms of neuromodulation on cortical excitability (Figure 1). We will first conduct a baseline measure of cortical excitability using a validated motor evoked potential (MEP) paradigm. Participants will then receive 20 minutes of one of four different stimulation conditions (active TMS, sham TMS, active taVNS, sham taVNS, paired taVNS/TMS, unpaired taVNS/TMS). MEPs will be then recorded immediately after stimulation, and every 10 minutes following for 30 minutes.

Neurostimulation



All participants enrolled in the pilot dosing trial will receive TST by a trained therapist in the **QBAR CORE**. TST will be administered 3 times per week for 4 weeks (12 total sessions). Each session will last 1 hour, and participants will be connected to EMG electrode arrays that will sense movements while the affected limb is trained in functional tasks like reaching forward to hold a glass and drinking from it, picking up and using objects, fine motor task and dexterity training. During TST, taVNS will be delivered in a movement-gated fashion.

Stimulation Parameters.

rTMS: 20 Hz rTMS will be delivered (using Magventure X100 system) to the motor hot spot of the left M1

region at 90% of rMT for 2.5 seconds ON and 10 seconds OFF. This will be repeated 40 times, for a total of 2,000 pulses of stimulation over 20-minutes. The stimulation target will be digitally marked using Brainsight neuronavigation for inter- and intra-session targeting validation.

taVNS: taVNS will be delivered (using a Digitimer constant current stimulation system) at the optimal stimulation parameters determined by our group (25Hz, 500us pulse width, 200% perceptual threshold) targeting the left anterior wall of the ear canal at a 50% duty cycle for 20 minutes.

Paired taVNS/TMS: We will synchronize taVNS with rTMS using MATLAB written software (Figure 2a). This software will deliver active/sham taVNS (25Hz, 500us PW, 200%PT) concurrently with active/sham 20Hz rTMS (2.5s ON, 10s OFF, 90% rMT) targeting the left M1 region (Figure 2b).

Unpaired taVNS/TMS: In this condition, active 20Hz rTMS (2.5s ON, 10s OFF, 90% rMT) will be delivered with active taVNS will be delivered in 2.5s trains during the rTMS using MATLAB written software. This software will deliver taVNS (25Hz, 500us PW, 200%PT) concurrently with 20Hz rTMS (2.5s ON, 10s OFF, 90% rMT) (Figure 2b).

Sham Controls:

rTMS sham - We will use the magventure rTMS sham procedure in which a sham coil is placed on top of scalp stimulating electrodes which will be placed on the scalp on or near the motor cortex. This setup mimics the sensation of rTMS, and participants cannot tell which condition they are receiving beyond chance.

taVNS sham – We will use a sham similar to that reported in our prior work, with electrodes placed on the earlobe – an ear target with limited to no ABVN innervation.

Collected Measures :

MEPs using the Motor Cortex Excitability Recording Paradigm

Resting and active motor threshold will be found using PEST, and automated algorithm used to determine threshold. EMG recordings using Ag/AgCl electrodes will be placed on the subject's abductor pollicis brevis (APB) muscle in order to record motor evoked potentials (MEPs). The EMG recording electrodes will be connected to a standard Cambridge Electronics Device (CED) MEP system and MEPs will be recorded and analyzed with the associated Spike2 software. The level of stimulation required to produce a MEP of 1mV will be determined prior to collecting baseline MEPs.Up to 80 Baseline MEPs will be collected at the pre-determined stimulation output for 1mV. After the 20-minute randomized stimulation condition, up to 40 MEPs will be collected immediately after stimulation and at 10minute intervals for 30 minutes.

Estimated Difficulties, Limitations and Time Frames

Estimated Difficulties. Healthy control MEP studies have been conducted in our laboratory for over 20 years – with minimal difficulty. For this particular study the estimated difficulty will likely be minimizing dropout over 5 experimental visits.

Limitations. There are two potential limitations with these studies. The first is tolerability of electrical nerve stimulation of the tragus and earlobe. Although we do not anticipate any issues, drop-out may be an issue due to discomfort of the stimulation.

Estimated Time Frames. We plan on completing this study over the next 6-8 months.

11.0 Data Management

Limited demographic and personal health history data will be collected during the phone screen in order to screen out participants with conditions that might confound the research or put them at risk for an

adverse event. All screening data will be kept in a binder in the locked office in the Brain Stimulation Lab as per the requirements of the IRB. Screening data collected from participants who do not qualify for the study will be securely destroyed.

Power Calculation: Our proposal utilizes a within-subject design, in which each subject will be their own control. Using the low end of a range of effect sizes (derived from 0.06 partial eta) from prior excitatory TMS/MEP studies (11-13) the proposed study will be sufficiently powered to detect a change in MEP magnitude due to an experimental intervention (paired active/sham rTMS, active/sham taVNS, unpaired taVNS/TMS) using a one-way ANOVA at 80% power and 5% significance level.

12.0 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 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 file cabinets or on secure servers designed for use and access by Brain Stimulation Lab members only.

An independent Data Safety Monitoring Board (DSMB) will be formed to advise the study investigators. The DSMB will review and evaluate accumulated study data to ensure safety. They also will make recommendations concerning continuation, modification, or termination of any of the taVNS/TMS studies. It will be composed of Dr. Baron Short, MUSC psychiatrist with expertise in transcranial magnetic stimulation (TMS); Dr. Jeff Borchardt, MUSC associate professor and assistant provost with extensive VNS, TMS, and tDCS experience; Dr. Andrew Mannet, MUSC Psychiatrist with expertise in TMS.

The DSMB will review all the data from the study in order to ensure safety of participants. 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 and to the DSMB.

13.0 Risks to Subjects

<u>taVNS:</u>

taVNS is nothing more than transcutaneous electrical nerve stimulation (TENS) of the auricular branch of the vagus nerve that innervates the ear. Although this novel therapeutic modality is still in the development and optimization process, risks are a combination of those to be expected by both the peripheral TENS and implantable cervical VNS.

TENS devices are FDA approved for pain relief and are available over the counter. The main risks associated with TENS are electrical hazards that may result in user discomfort or injury. The unit used in these studies (Digitimer DS7AH) is a 510(k) cleared electrical stimulator that meets the rigorous electrical standards of the FDA. Skin irritation, redness, or inflammation may occur under the stimulating electrodes if TENS current is delivered for a prolonged period of time.

Implantable cervical VNS is FDA approved for the treatment of intractable epilepsy and treatment resistant depression. Cervical VNS has risks associated with the procedure of implanting the nerve, and

the surgery. None of those apply here. taVNS does has some minimal risks that are due to the actual stimulation of the nerve within the neck such as skin irritation. taVNS also has associated risks that may arise from the direct brain effects stimulating the vagus nerve. These theoretical risks associated with neuromodulation of the parasympathetic nervous system would also be applicable in the administration of noninvasive taVNS. They are the following: reduction of heart rate, blood pressure, and vasovagal syncope.

Given the minimal risk both of these already FDA approved methods introduce, we suspect taVNS will be a very safe procedure. taVNS is not intended to be a therapy for currently existing conditions and all subjects will be healthy controls with no previous history of neurological disorders or trauma.

TMS:
The TMS coil makes noise, much like a loud pop when it produces its magnetic energy. You may or may not feel your thumb twitch depending on the strength of the TMS pulse, but you might also feel your facial muscles twitch slightly just around your left eye. This twitch is just as brief as the thumb twitch and is a result of the TMS directly stimulating the facial nerves and muscles that run directly under your scalp. It is not painful. TMS can cause heating or movement of metallic objects in or near the head. In addition, the inactivation of pacemakers, medication pumps, cochlear prostheses and other implantable hardware may occur. Magnetic media such as credit cards, etc. and watches near the coil may also be damaged. To minimize this risk the researchers will have asked you about any metal implants which would exclude you from the study. There is a known risk of inducing a seizure during rTMS [57, 58] however these are very rare (<0.1% of all cases) and often happen during acute alcohol withdrawal or lack of sleep – both of which will be monitored in healthy individuals.

Unknown Risks: Although taVNS and TMS are considered very safe, they are still an experimental procedure that has not been approved by the FDA. The Principal Investigator will let you know if they learn anything that might make you change your mind about participating in the study

Loss of Confidentiality: There is always a risk of breach of confidentiality which may result in your personal information being seen by people outside of this study. The study team will ensure safety of your personal information and all of your information will be de-identified and coded to mitigate these risks.

Risks of Randomization: Because participants may not receive active stimulation each time, the risks vary by randomization. Risks are greater associated with conditions in which the randomized participant receives active intervention rather than placebo.

14.0 Potential Benefits to Subjects or Others

There are no potential benefits to the subjects in this study, however the benefit to society may be a better understanding of the mechanism of taVNS in facilitating motor excitability and potentially developing rapid treatments for stroke recovery.

15.0 Drugs or Devices

The closed-loop taVNS and TMS stimulation systems are stored at the MUSC Brain Stimulation Lab and will be “dispensed” by the PI, study staff, or occupational therapist during study visits.

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