STU#: STU00207734

PROTOCOL TITLE: The impact of yoga-based physical therapy on heart rate variability for individuals with traumatic brain injury: a pilot study

PRINCIPAL INVESTIGATOR:

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STUDY SUMMARY:

Investigational Agent(s) (Drugs or Devices)	n/a
IND / IDE / HDE #	n/a
Indicate Special Population(s)	☐ Children ☐ Children who are wards of the state ☒ Adults Unable to Consent ☒ Cognitively Impaired Adults ☐ Neonates of Uncertain Viability ☐ Pregnant Women ☐ Prisoners (or other detained/paroled individuals) ☐ Students/Employees
Sample Size	30
Funding Source	Shirley Ryan AbilityLab (SRALab)
Indicate the type of consent to be obtained	☒ Written ☐ Verbal/Waiver of Documentation of Informed Consent ☐ Waiver of HIPAA Authorization ☐ Waiver/Alteration of Consent Process
Site	☐ Lead Site (For A Multiple Site Research Study) ☒ Data Coordinating Center (DCC)
Research Related Radiation Exposure	☐ Yes ☒ No
DSMB / DMC / IDMC	☐ Yes ☒ No

OBJECTIVE:

Objective #1: This pilot study aims to explore if a yoga-based physical therapy session would promote improved (increased) heart rate variability (HRV). The results of this pilot study will inform a larger-scale study of the effects of regular participation in a yoga-based program as an adjunct to traditional physical therapy.

Hypothesis #1: Individuals who participate in 1 hour of a yoga-based physical therapy session in a group setting will demonstrate a significant improvement in heart rate variability during the session when compared to heart rate variability during 1 hour of a conventional PT session and 1 hour of seated rest in a relaxing environment.

Objective #2: Determine whether a yoga-based physical therapy session would impact present-state anxiety, fatigue, or agitation and/or sleep quality.

Hypothesis #2: Individuals who participate in 1 hour of a yoga-based physical therapy session in a group setting will demonstrate a significant improvement in self-reported present-state self-reported anxiety and fatigue, observation-based agitation (when agitation is present), and sleep quality when compared to the same measures after 1 hour of a conventional PT session and 1 hour of seated rest in a relaxing environment.

BACKGROUND:

Traumatic brain injury (TBI) is a significant cause of morbidity, mortality, and disability throughout the world, with an estimated incidence of 180-250 per 100,000 population at risk per year in the United States alone.[1-2] Despite an increased understanding of the pathophysiology of TBI and the mortality rate after TBI significantly reducing in recent years with advances in life-saving medical treatment, the incidence and severity of disability resulting from TBI has not considerably changed.[2-3]

Many individuals with TBI experience anxiety and depression. A striking 27% of individuals post-TBI meet Diagnostic and Statistical Manual for Mental Disorders (DSM) IV criteria for depression at 1 year after TBI.[4] HRV is an indicator of autonomic nervous system (ANS) activity/control, and has been found to be a surrogate marker for anxiety and depression.[6-10] A person with high HRV is considered to have “vagal dominance”, which is positively associated with aerobic fitness, stress resilience, psychological/physiological flexibility, and negatively associated with cardiovascular disease, neuronal atrophy, negative affective states, and maladaptive stress responses.[11] There is evidence that some individuals with TBI have demonstrated persistently low HRV, even up to 5 years after TBI.[12-13] Liao et al correlated low HRV with anxiety in individuals after mild TBI[14], while Sung et al correlated low HRV with both anxiety and depression in individuals after mild TBI. [15]

Individuals with TBI also experience significant problems with sleep, which may worsen underlying anxiety and depression.[16] Individuals after TBI subjectively report increased sleepiness and poorer perceived sleep quality, bolstered by data demonstrating reduced rapid eye movement (REM) sleep time and shorter overall sleep duration versus healthy controls.[17] These problems with sleep also affect cognitive and physical performance in therapy, and possibly long-term outcomes and quality of life.[18-20] Medications that are traditionally given for sleep, depression, and anxiety may have adverse effects on recovery following TBI. Given the high incidence of anxiety, depression, and sleep issues post-TBI, and the profound impact of

anxiety and depression on physical independence and functioning in TBI, this population may benefit from an alternative approach to rehabilitation.

There is growing body of evidence proposing yoga as an alternative medical approach to exercise and health maintenance in healthy individuals. Yoga practice involves integrating physical movements (*asanas*), breathing exercises (*pranayama*), and meditation to increase balance, strength, coordination, and flexibility in the context of increasing self-awareness and promoting relaxation.[21-22] Additional ambience elements are commonly observed in the practice of yoga to maximize relaxation, including dimmed lights and gentle, calming music playing in the background. For the purposes of this study, "yoga" will be defined as: integrating *asanas*, *pranayamas*, meditation, and a calming ambience to promote relaxation and increases in balance, strength, coordination, flexibility, and self-awareness.

When compared with control groups completing traditional exercise protocols that do not integrate breathing and mindfulness-based practices, yoga programs have been shown to reduce depression, anxiety, and stress.[23-25] In adults with insomnia, participation in a regular yoga group has also been shown to improve overall sleep quality and sleep efficiency, latency and duration, which correlated with improvements in self-reported fatigue, depression, anxiety and stress, enabling increased participation in functional roles.[26] Yoga has also been shown to increase heart rate variability, which indicates a shift in autonomic nervous system dominance from sympathetic to parasympathetic.[11,27] A comprehensive review by Tyagi et al found that sufficient evidence suggests that yoga affects cardiac autonomic regulation by increasing HRV during yoga practices in healthy, non-regular yoga practitioners, and in regular yoga practitioners, at rest.[11]

The effects of yoga in neurological populations are being increasingly studied, particularly in patients after stroke (CVA). Studies have demonstrated improvements in balance and gait speed, as well as subjective reports of feeling calmer and more "connected", and having increased acceptance of disability/new physical abilities.[28-33]

There are limited studies exploring the use of yoga-based programs in patients with a history of traumatic brain injury.[34] A study by Donnelly et al involved community-dwelling individuals with chronic TBI participating in a twice-weekly, 8-week yoga program. The yoga program was associated with improved overall QOL.[35] Several case studies with individuals with chronic TBI participating in a yoga program have reported improved QOL, reduced depression/improved mood, and improved psychological well-being, strength, endurance, and balance confidence.[36-40] None of the above stated studies have taken place in the acute rehabilitation setting, leaving a void in the literature regarding early integration yoga as an alternative technique to combat the development of anxiety and depression sequelae of TBI.

INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria:

- Individuals diagnosed with traumatic brain injury admitted to the Shirley Ryan AbilityLab (SRALab)
- Age 18 or older
- Able and willing to give written consent or has an identified medical proxy willing to give written consent on behalf of the individual

- Able to follow commands consistently with a reasonable amount of verbal or visual cues in order to participate in a 60-minute physical therapy session in a group setting
- Able to attend to a task with reasonable amount of verbal or visual cues in order to participate in a 60-minute physical therapy session in a group setting
- Behaviorally appropriate for a group setting in terms of verbal or physical escalation/aggression

Exclusion Criteria:
- Serious cardiac conditions (arrhythmias) or neurological comorbidities (such as multiple sclerosis, Alzheimer's disease, Parkinson's disease, etc.)
- Pregnant or nursing
- Skin allergies or irritation; open wounds in the areas that the sensors would be applied to
- Utilizing a powered, implanted cardiac device for monitoring or supporting heart function (i.e. pacemaker, defibrillator, or LVAD)
- Non-English speaking patients, due to necessity for an interpreter to be present constantly interpreting, which could impact the low-stimulation setting of the intervention
- Aphasia or any difficulties in accurately self-reporting

PARTICIPANT POPULATION

The study will enroll up to 30 inpatient subjects on a rolling basis as they are admitted with traumatic brain injuries over a 12 month period at the SRALab. Data will be analyzed within approximately 12 months from the date of the initiation of data collection.

STUDY INTERVENTION:

The study will be a randomized, controlled, single-blinded, crossover design with three conditions: condition A will consist of 1 hour of yoga-based physical therapy session in a group setting; condition B will consist of 1 hour of one-on-one conventional PT; condition C will consist of 1 hour of seated rest in a relaxing environment in a group setting. In an attempt to minimize the impact of changes in medications which could impact sleep, conditions will occur on three consecutive days, and the interventions will take place at the same time every day. Subjects will participate in a yoga-based PT group at least once prior to participation in the 3 conditions. This protocol design was chosen to control for the potential of heightened awareness in a novel environment/experience which could impact the heart rate variability data if it were to be collected during the first experience of a yoga-based PT session.

Condition A: The yoga-based physical therapy session will take place in an enclosed, quiet space to minimize outside noise or distraction. The lights will be dimmed, and light, instrumental, calming music will be played throughout to contribute to a relaxing ambience which is atypical of a standard physical therapy session. Participants will be seated in a standard chair facing the clinician-researcher physical therapist, who will lead the group. All yoga-based PT sessions will be led by the same physical therapist to maximize between-session consistency. The group will consist of approximately 2-5 individuals depending on the physical capabilities and assistance levels required. A trained research assistant will also be present to provide additional cueing to subjects when required. The session will begin with 5-7 minutes of an introduction to posture, *pranayama* (foundational breath-based exercises), and instruction on proper recruitment of core musculature, followed by approximately 45 minutes of *asanas*, or physical postures. *Asanas* will be modified according to each individual's physical abilities to optimize safety and ensure the postures are appropriately challenging. For example,

if an individual requires moderate assistance or greater on the Functional Independence Measure (FIM) to perform the posture in standing, the posture will be completed from a seated level with suggested modifications to ensure sufficient challenge (such as reduced upper extremity support or closing the eyes). The basic elements of postures are similar to that of traditional physical therapy balance exercises, such as transitional movements (sit to stand), narrow stance, single leg stance, and lunging, with additional modifications placed to increase the challenge (such as closing the eyes or reducing upper extremity support). Cues will be provided throughout to pair appropriate breath cycles with appropriate postures consistent with a standard, able-bodied yoga program; for example, exhaling when flexing the trunk downwards and inhaling when reaching upwards. Participants will also be regularly cued for appropriate core engagement and posture. Rest breaks will be provided as needed based on clinician judgement of subject exertion level. The session will close with a 4-5 minute *savasana* performed in a supine or seated position pending patient physical abilities, which consists of progressive relaxation, guided meditation, and guided motor imagery.

Condition B: Subjects will engage in 1 hour of a conventional PT session (or “treatment as usual”) led by a different physical therapist than who is leading the yoga-based session to minimize bias. All conventional PT sessions will be led by the same physical therapist to maximize between-session consistency. There will be no restrictions on what can and cannot occur during conventional PT sessions in order to accurately represent and preserve the wide range of treatments that may occur during a physical therapy session in the inpatient setting. The sessions will be individual, 1:1 sessions to mimic a standard PT session; <5% of therapies in the TBI population at SRALab are in a group setting. Examples of what may occur as part of the conventional PT session include, but are not limited to: gait (over ground or treadmill; includes stairs), static or dynamic standing balance (such as sidestepping, backwards ambulation, braiding, obstacle negotiation), functional mobility (such as transfers, bed mobility, wheelchair mobility), or therapeutic exercise (such as body-weight strengthening exercises or stationary cycling).

Condition C: Subjects will engage in 1 hour of seated rest in a relaxing environment in a group of approximately 2-5 individuals. This session will occur in the same enclosed, quiet space as condition A to minimize outside noise or distraction and to reproduce environment of condition A. The lights will be dimmed, and the same light, instrumental, calming music will be played throughout to contribute to a relaxing ambience. Subjects will be instructed to rest quietly.

PROCEDURES INVOLVED:

Admissions to the traumatic brain injury service of Shirley Ryan AbilityLab will be reviewed on a weekly basis, and eligible patients will be approached to attain assent/consent.

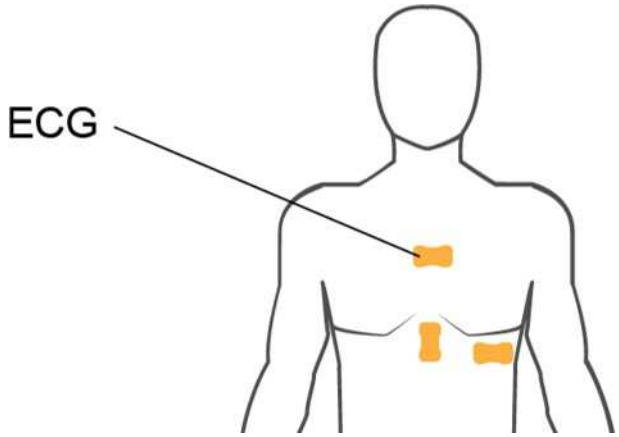
Patients will be randomized as to which condition they participate in first. Subjects will be instructed not to eat or drink caffeine within 1 hour of participating in a condition. A trained researcher will apply three MC10 sensors to the chest in the following locations (see Figure 1) by: left parasternal and midclavicular line, left parasternal line, and left mid-axillary line. The sensors to monitor HRV via electrocardiogram (EKG) are from the BioStampRC Discovery Kit MC10, Inc., and are research-grade, non-invasive, wireless, wearable sensors. For each sensor location, the skin will be prepped and cleaned using alcohol wipes. Sensors are placed on the skin using adhesive stickers that minimize irritation. Medical dressing (Tegaderm, 3M) may also be used to ensure adhesion and proper contact with the skin. Sensors will be cleaned with soap and water before and after use. Vital signs will be measured.

A research staff member will administer the pre-intervention anxiety outcome. Agitated Behavior is monitored using the Agitated Behavior Scale administered by a registered nurse, in circumstances where appropriate; see below for more details. All study measures will be performed in the patient's room so as to blind the researcher from what condition he or she is prepping to participate in. Subjects will be transported to the designated therapy area on the 25th floor by a different trained researcher.

The subject will participate in the assigned condition for that day as determined by randomization (see above for specifics on the three conditions), and HRV will be monitored throughout the condition. Immediately following the 1-hour condition, the sensors will be removed by a trained researcher and vital signs will be taken. The patient will be transported back to his or her room. The research staff member will then meet the patient in their room to administer self-reported anxiety and fatigue outcome measure. The Agitated Behavior Scale will then be administered by a registered nurse, only in circumstances where this outcome measure is appropriate; see below for more details. Subjects will complete forms as able, but if they require physical assistance to fill out or verbal assistance in reading the questions, such assistance will be provided. Sleep quality will be captured in all conditions by an activity monitor To compare session days to a broader picture of the patient's sleep and activity cycles, the patient will wear the activity monitor from as early as immediately after consent until the morning after they complete their last session. Research staff will don the activity monitors at the time of consent, and doff them the morning after they complete the last session. Due to scheduling constraints (ie, subjects having to participate in the yoga group at least once prior to data collection, the yoga group only taking place once per week, the time required to schedule the group and data collection sessions, and the randomization scheme), the time from consent until the last day of data collection could be as little as seven days or as long as fourteen days depending on what day the patient consents. The subject is permitted to remove the activity monitor if desired throughout the day (for example, when showering), but to minimize the chances of the monitor being lost or not being re-donned, it is recommended that the monitor be kept on.
All sessions will be supervised by a physical therapist. Research staff will be responsible for all sensor recording practices, such as instrumenting the sensors and marking therapy activities on a computer tablet using the BioStampRC software. Research staff will also keep a written log of activities as they are undertaken during the assessments, including notable events, amount and type of assistance, or use of external devices. Logs will be consulted during analysis to compare with the timestamped sensor data.

Audio/video recording may be utilized in order to allow a registered yoga therapist to validate the yoga-based program led by the researcher-clinician physical therapist. The recordings would only be viewed by the physical therapist and registered yoga therapist, and destroyed after publication of the research. The videos would be stored in a password-protected device; the yoga therapist and physical therapist would be the only individuals with access.

Figure 1: BioStampRC placement



DESCRIPTION OF CLINICAL ASSESSMENTS

All assessments will be performed by a trained researcher or registered nurse.

Anxiety: Present-state anxiety will be quantified with the use of the modified, 6-item short-form of the state scale of the Spielberger State-Trait Anxiety Inventory (STAI). [41] The full-form STAI is a 40-question anxiety measure typically applied in psychology research. Twenty questions measure state anxiety, or how one feels at the present moment, while twenty questions measure trait anxiety, or how one generally feels. The 6-item short-form focuses only on state anxiety, and was created to reduce burden for populations who are unable to complete lengthy scales. The short form has been found to be as valid as the 20-question state anxiety form of the STAI, and demonstrates acceptable reliability. [41]

Neurocognitive Fatigue: A component of the Global Fatigue Index (GFI) will be utilized to assess present-state fatigue. The GFI is a measure developed from the Multidimensional Assessment of Fatigue (MAF) Scale, and has been validated and widely used in the TBI population.[42-44] Only the first three questions ("To what degree have you experienced fatigue?", "How severe is the fatigue which you have been experiencing?", and "To what degree has fatigue caused you distress?") will be utilized given that the remaining questions are related to chronic fatigue. In order to capture the present-state fatigue, the wording of the questions will be modified slightly to reflect present-state feelings. The stem, which reads, "Degree of Agreement (please circle number from 1 to 10, with 1 = not at all and 10 = a great deal)", will also be modified to increase clarity for cognitively impaired subjects to read, "1=None, 2=A little bit, 3=A moderate amount, 4=Quite a lot, 5= Extreme".

Agitation: This outcome will only be collected when the patient presents with agitation and is actively being assessed with the Agitated Behavior Scale (ABS) on a regular basis by the nursing staff. The ABS measures behavioral aspects of agitation during the acute phase of recovery from acquired brain injury including aspects of aggression, disinhibition, and lability.[45] It is a 14-item instrument, each rated on a scale of 1-4, with maximum score being 56 points. Subscale scores for disinhibition, aggression, and lability can be calculated, in addition to a total

score. 10 minute observations are reliable and 30 minute observations have been deemed reliable and valid. [45] This measure is recommended by the TBI-EDGE Task Force.

RECRUITMENT METHODS

This study coordinator will review patients admitted to the inpatient units at SRALab with a diagnosis of TBI on a weekly basis. Potential research subjects will be identified based on inclusion and exclusion criteria using the Cerner application. Participants' demographics and health information will also be collected from Cerner, including age, sex, race, language, and medical history. If deemed appropriate to safely participate in a physical therapy group from a cognitive, behavioral, and physical standpoint, they will be considered for participation in the study. Prior to approaching prospective subjects and informing them of the study, the study coordinator will ask the patient's attending physician whether patient has the capacity to consent for participation in the study. If the patient does not have the ability to provide consent for participation in the study themselves, their medical proxy or next of kin will be approached for consent. Subjects will be asked for assent to participate in all cases.

COMPENSATION FOR PARTICIPATION IN RESEARCH ACTIVITIES
There will be no compensation for participation in this research study.

WITHDRAWAL OF PARTICIPANTS
Subjects will be withdrawn from the study in the event of a medical event or complication that may alter the inclusion/exclusion criteria or which limits the patient from safely completing the remainder of the study, or at the discretion of the Principal Investigator (PI). The researchers reserve the right to discontinue study participation for any individual or for the study as a whole at their discretion.

Subjects can voluntarily discontinue the study at any time. The PI, Dr. David Ripley, will be notified.

RISKS TO PARTICIPANTS
All sessions will be under supervision of a trained physical therapist. Physical assistance or cueing will be provided as necessary for safety and balance. Vital signs will be monitored as needed before and after physical exertion and during activities. All subjects will be permitted to stop physical activity or rest at any time during the study.

There is a risk of muscle soreness due to increased physical activity during testing sessions. All subjects will work with trained researchers and clinicians. Adequate rest will be given and subjects will be monitored for verbal or visual signs of fatigue or discomfort. The risk of soreness is similar to that during any clinical inpatient therapy session.

There is a risk of falling due to the physical activity and balance challenges involved in the yoga group and the conventional PT session. The risk of falling will be reduced by having each participant supervised during training and testing by a clinician or researcher trained in all testing procedures. During these assessments, the participant will use a gait belt for safety. The risk is similar to that during any clinical inpatient therapy session.

There is a risk of irritation to the skin from wearing the sensors. This risk will be reduced by minimized by excluding people who have a known allergy and discontinued use if skin irritation occurs.

POTENTIAL BENEFITS TO PARTICIPANTS

Possible benefits include improved heart rate variability, anxiety, sleep quality, and fatigue.

DATA MANAGEMENT AND CONFIDENTIALITY/DATA AND SPECIMEN BANKING

All identifiable personal information gathered for this study will be kept in a locked secure file cabinet. Only personnel who are directly responsible for data collection and analysis will have access to the key. Subjects will be assigned a subject number at the beginning of the study. Study data will be de-identified and added by subject number into a research database. All personal information collected for this study will be destroyed as soon as feasible (approximately 2 years) following completion of the study and publication of study results.

Data from the BioStampRC sensors will be accessed via a private MC10 Inc. Investigator Portal, a cloud-based system, and data from the activity monitors will be accessed via a cloud-based storage system. Both cloud-based systems comply with security best practices at all system levels. Data will be de-identified when using the BioStampRC and activity monitor collection systems, so information stored on the private Investigator Portal cannot be linked to subjects. Upon completion of data collection phase of the study, all data will be transferred to password- and firewall-protected internal servers and removed from the Investigator Portal.

The data will be reviewed by an assessor blinded to condition and to any identifiable patient data. The data will be reviewed along with a blinded statistician who will aide in determining the appropriate statistical tests to perform given the objectives of the study.

PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS

Every possible precaution will be taken to protect the privacy interests of subjects. Participation in this study is completely voluntary. Trained research personnel will explain the purpose of the study, intended use of subject's personal health information, and precautions taken to keep the study information and data confidential.

CONSENT PROCESS

Informed consent will take place at SRALab in the inpatient floor with authorized study personnel. Trained research personnel will guide the subject through consenting process. Before recruitment and enrollment onto this study, the subject and his or her medical power of attorney when applicable (see "Vulnerable Populations" below) will be given detailed explanation of the purpose, time line, commitment, procedures, data handling and privacy and confidentiality of information pertaining to the study. Each consent form will include all the relevant elements as approved by the Northwestern University Institutional Review Board. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form. Subjects will be consented with a new consent form if changes are made to the protocol. Prior to a patient's participation in the trial, the written informed consent form must be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

VULNERABLE POPULATIONS AND ALTERATION OF CONSENT PROCESS

Prospective subjects for the study may still be in a state of post-traumatic amnesia or otherwise impaired in the full capacity to give consent to participate in a research study. The study coordinator will approach the patient's attending physician who will determine eligibility and capacity to consent. If the patient does not have the capacity to consent, the patient will be asked to provide assent, and formal written consent will be obtained from the patient's medical proxy.

SETTING:
The study will occur at the Shirley Ryan AbilityLab, 355 E. Erie Street, Chicago IL, 60611 in the small gym or Ability Lab on 25th floor inpatient unit.

RESOURCES AVAILABLE:
There are medical resources including a resident on call and nursing staff available 24 hours a day, 7 days per week if needed in case of an emergency.

PROTECTED HEALTH INFORMATION (PHI AND HIPAA)
The complete medical history of the inpatients, including physical findings, radiological reports such lesion size, location, type, medications and therapist-assessed clinical outcomes may be used to associate with biometric and movement obtained from the wearable sensors. Subjects' records will be kept completely confidential. Data will be collected and kept confidential and compliant with HIPPAA requirements. Research data will be de-identified and stored in locked cabinets in the lab with access only to research staff. Electronic data will be deidentified and kept on secure, password protected files and password protected computers.

SHARING RESULTS WITH PARTICIPANTS
If a subject is interested in hearing the results of his or her collected data, this information can be shared by Dr. David Ripley at (312)-238-1000, or Kelly Krese at (312)-238-5938, at any time.

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