STU#:

PROTOCOL TITLE: Enhancing cortical-hippocampal functional connectivity as a novel means for relieving chronic low back pain

PRINCIPAL INVESTIGATOR:
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VERSION DATE: 02 Jun 2021
(Include the version date here and in the footer.)

STUDY SUMMARY:

Investigational Agent(s) (Drugs or Devices)	NA
IND / IDE / HDE #	NA
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	16
Funding Source	NIDA
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

LIST OF ABBREVIATIONS

ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
BDI	Back Depression Inventory
BDI-II	Back Depression Inventory, Second Version
BP	Brain Properties
CBP	Chronic Back Pain
CESM	Cognitive Emotional Sensory Motor
CNS	Central Nervous System
CTA	Chicago Transit Authority
dMRI	diffusion Magnetic Resonance Imaging
EDW	Enterprise Data Warehouse
FC	Functional Connectivity
GMV	Gray matter volume
HIPAA	Health Insurance Portability and Accountability Act
Hipp	Hippocampus
Hz	Hertz
MQSIII	Medication Quantification Scale, third version
MRI	Magnetic Resonance Imaging
NAc	Nucleus Accumbens
NIH	National Institutes of Health
NMG	Northwestern Medical Group
NMH	Northwestern Memorial Hospital
NRS	Numeric Rating Scale
NU	Northwestern University
PAG	Periaqueductal Gray
PDQ	Pain Detect Questionnaire
PHH	Personal Health History
PHI	Protected Health Information
PIDs	Participation identification numbers
REDCap	Research Electronic Data Capture
rsfMRI	Resting State Functional Magnetic Resonance Imaging
rTMS	Repetitive Transcranial Magnetic Stimulation
SC	Central Sensitization
SEM	Structural Equation Modeling
TJS	Thomas Jack Schnitzer
TMS	Transcranial Magnetic Stimulation
VBM	Voxel-based morphometry

KEY ROLES AND CONTACT INFORMATION

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OBJECTIVES:
(*Describe the purpose, specific aims, or objectives. State the hypotheses to be tested*.)

Chronic back pain (CBP) can last from months to a lifetime, severely impacting patients' quality of life. Based on our human brain imaging studies and preclinical findings, the hippocampus and its network are associated with pain and pain experience in patients with chronic pain. In this study we aim to test whether a non-invasive enhancement of dorsal hippocampus activity leads to networks alteration that can modulate pain in CBP patients.

Aim 1: To investigate whether a novel target, dorsal hippocampus, indirectly stimulated using high frequency rTMS, will lead to an increase in hippocampal network connectivity that can modulate pain, as compared a sham control rTMS, in CBP patients.

We hypothesize that changes in pain from baseline to post-stimulation will be superior for hippocampal-target than for control stimulation (sham). Pain is primarily assessed by daily ratings on our phone app; additional questionnaires will be used as secondary exploratory outcomes.

BACKGROUND:

Pain is the primary reason why people seek healthcare. Everyday millions of Americans are either partially or totally disabled due to pain. If untreated, this pain can lead to depression, insomnia, depressed immune function, changes in eating patterns, impaired cognitive function, and other long-term deleterious effects commonly associated with chronic pain[1–3] . Chronic back pain constitutes the major form of chronic pain, with a prevalence as high as 70-85% in adults at some time in their lives [4]. In the US, low back pain is the most common cause of activity limitation in adults younger than 45 years of age and the second most frequent reason for physician visits[1,5]. Estimates from other countries support the fact that low back pain is one of the major - if not the major - cause of work absence, and therefore results in a significant burden to both the economy and health care system.

Current treatments for CBP involve the use of nonsteroidal anti-inflammatory drugs, antidepressants, and/or anticonvulsants or opioids. These carry relatively high risks yet show limited success rates[6], leading investigators to explore non-invasive interventions that in combination with conventional treatments, may produce greater pain relief in CBP [7,8].

Chronic back pain is associated with many negative affective mood disorders [9], and cumulative evidence suggests an association of hippocampal networks and chronic pain. Previous research performed by our group has shown the hippocampal circuitry being involved in the transition from acute to chronic pain, and hippocampal mechanisms such as diminished hippocampal neurogenesis [10]. Moreover, abnormal glutamatergic activity was previously described in animal chronic pain models and bilateral hippocampal deactivation during innocuous stimulation in neuropathic patients [11,12]. Therefore, our group conducted an animal study using chemogenetics or direct GLU injection to increase dorsal hippocampal glutamatergic activity and modulate pain. This demonstrated the analgesic effects of hippocampal stimulation; since increases in excitability of dorsal hippocampal neurons altered resting state connectivity (rsfMRI) within hippocampal networks that are specifically related to neuropathic behavior (tactile allodynia), thus indicating the potential for hippocampal stimulation in the management of chronic pain [13]. Considering the previously established role of the hippocampus in pain perception, and its

morphological changes in chronic pain, there is now impetus for investigating hippocampal excitation in chronic pain relief. With this in mind, we reason that in humans, by modulating local hippocampal circuits, we can directly target chronic pain.

In this pilot study, we aim to indirectly stimulate the dorsal hippocampus to increase hippocampal connectivity and modulate pain. We will use rTMS to stimulate an area of the parietal cortex with high functional connectivity to the hippocampus, using seed-based connectivity analysis of rsfMRI data, in order to modulate hippocampal-mediated networks. It is notable that targeting hippocampal excitability using rTMS is an approach that we have pioneered. The hippocampus is not directly accessible to rTMS. We use cortical “access windows”, which are stimulation-accessible areas of the cortex that have high connectivity with the hippocampus and therefore stimulation applied to these areas can indirectly influence the hippocampus. In several experiments. We have shown that this method increases excitability and rsfMRI connectivity of dorsal hippocampus, leading to long-lasting improvements in hippocampal-dependent function[14–17]. We hypothesize that dorsal hippocampal stimulation will lead to analgesic effects in CBP.

In line with the promising preclinical results we report, in this study we will collect preliminary data to systematically test whether the modulation of hippocampal network changes the experience of pain in CBP patients.

STUDY ENDPOINTS

This is a mechanistic study; therefore, the main study aim is to show that the hippocampal stimulation leads to functional connectivity changes across series of hippocampal networks and how these connectivity changes are correlated with pain decrease.
The secondary outcome will be changes in pain ratings. The effects of the brain stimulation will be measured by daily pain ratings (painApp) and questionnaires, using our in-house pain app. As we collect these outcomes repeatedly, we will have changes in pain immediately after the stimulation session and also over the next 2-weeks.We will test immediate and 2-weeks changes in painApp ratings relative to baseline. Questionnaire analyses, and other time course analyses of painApp data will be treated as exploratory in nature.

STUDY INTERVENTION(S) / INVESTIGATIONAL AGENT(S):

Brain Stimulation

For the brain stimulation we will use Repetitive Transcranial Magnetic stimulation (rTMS) The sessions will be performed at either the CTI or the LHN. Repetitive TMS parameters are determined based on the allowable dosage of rTMS delivery, calculated based on published standards for experimental rTMS protocols, and in accordance with standard operating procedures for rTMS [18,19]. Previous studies have shown that four or more rTMS sessions are needed to induce changes in the hippocampal network conectivity[20].

The brain stimulation can be delivery using different devices; in this project we will use a MagPro X100 stimulator connected to a MagPro Cool-B65 liquid-cooled butterfly coil (MagVenture A/S, Farum, Denmark). Resting motor threshold (M1-rTMS) will be determined during the visit 1 or visit 2 and used along the 10 visits. Single TMS pulses are delivered to the thumb-control area of the brain’s primary motor cortex and the pulse intensity required to reliably evoke movement of the thumb is determined. This value is used as each individual subject’s “motor threshold”, and stimulation is delivered at a proportion of the motor threshold.

The rTMS pulse sequences and intensities used are all within the published safety guidelines [21,22].
As different stimulation conditions (hippocampal, M1 or sham) will be delivered in each of the three rounds of stimulation, participants will be told that stimulations can feel and sound different. All participants will receive all the 3 modalities of stimulation following specific order (see details below).

- Stimulation Modality 1- Hippocampus-stimulation:

Repetitive TMS will be applied at 100% resting motor threshold intensity to a region of interest located in the parietal cortex, that will be determined based on its connectivity with the hippocampus. This stimulation consists of a series of 1,600 pulses administered as 2-second periods of 20 Hz pulse trains separated by 28-s inter-train intervals (~20 minutes for the entire daily stimulation session). The induced current field will be oriented perpendicular/anterior to the long axis of the gyrus encompassing the stimulation location.

- Stimulation Modality 2-Sham-stimulation:

Parameters will be identical to the hippocampus-stimulation, except that the coil will be flipped over to the sham side and a stimulating electrode will be attached to the skin near the parietal rTMS target location. This electrode will be used to deliver a small current mimicking real stimulation sensation, therefore participants cannot reliably discriminate physical sensations for real versus sham rTMS.

A trained co-investigator on the study will administer the rTMS. Prior to performing any study procedures, the study staff member will be trained in the techniques of rTMS as well as all aspects of the evaluations. This study staff member will then be evaluated by the PI of the study. The PI will then give confirmation that the co-investigator is qualified to administer the stimulation and the evaluations. Subjects are allowed to miss up to 1 stimulation visit in each treatment round, we will drop out subjects that miss more than 1 stim visit per round.

Stimulation modality sequences:

The order of the stimulation modalities will be different across subjects. Subjects will be randomly assigned to one of two possible groups/stimulation sequences (fig 1). Before enrollment starts, we will produce 18 envelopes containing the stimulation sequence (see below possible combinations; we expect to use only 16). The stimulation sequence will be kept in sealed envelopes; therefore, subjects will get their assignment according to the order of entrance in the study. The study coordinator will retain the original sequence list which will be kept in a locked place. The study staff who provides the stimulation TMS session will be the only un-ed personnel.

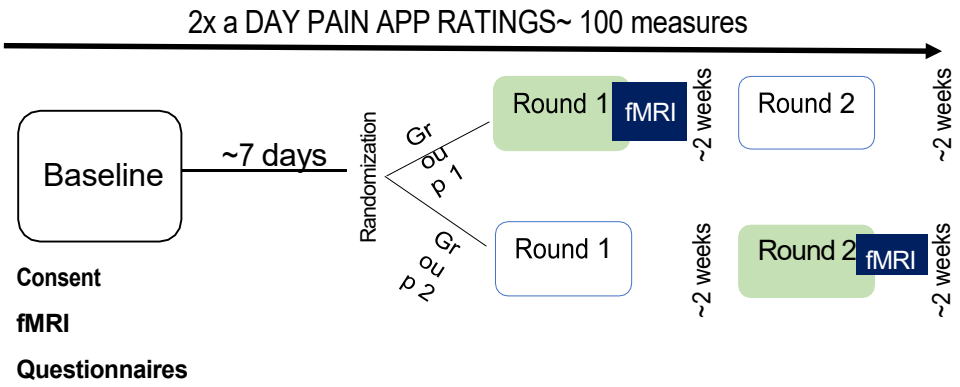

Figure 1: Study design and stimulation sequence. The subjects will be allocated to 1 envelop according to the entrance in the study. All participants will receive all the 2modalities of stimulation. Each round is composed by 5 daily session of stimulation, participants will not know which round is active and which is sham. Participants randomized to group 1 will have a second MRI at visit 6; and participants randomized to group 2 at visit 11.

PROCEDURES INVOLVED:

General Overview

Participants will be enrolled after meeting all inclusion/exclusion criteria including an NRS (0-10 pain score) >4/10 for back pain and no contra-indications to the rTMS stimulation and MRI exam.

Detailed Study Outline

- **Pre-screening Procedures:**

During the pre-screening process, the subject will contact a study staff (or vice-versa) usually via phone call or email. During this call, the co-investigator will discuss in greater depth the details of the study, explain the study procedures and encourage the subject to ask questions. In the privacy of the laboratory, the co-investigator will ask the subject questions from the following:

  - Phone screening questionnaire

- **Visit 1** - (Approx. Time: 2-3 hours)

Screening Procedures:

At Screening the PI and the co-investigators will conduct a review of inclusion/exclusion criteria to determine the subject's eligibility for enrollment. Study procedures will be reviewed with the subject, and documentation of informed consent will be obtained.

At Visit 1 the following procedures will be completed:

  - Discuss study-specific procedures with the subject;
  - Review inclusion and exclusion criteria, including list of current medications;
  - Obtain a signed and dated consent form;
  - Demographic Data;
  - Review the subject medical history with the study coordinator.

- Measure blood pressure, heart rate and respiratory rates will be measured.
- Measure height and weight
- Urine sample for illicit drugs test and pregnancy exam (if applicable);
- Fill out a screening form to make sure it is safe for the subject to have a brain scan and stimulation sessions. It is important that the subjects inform the study coordinator if they have any history of:
  - Metal fragments in their eyes or face.
  - Implantation of any electronic devices such as (but not limited to) cardiac pacemakers, cardiac defibrillators, cochlea implants or nerve stimulators.
  - Surgery on the blood vessels of their brain or the valves of the heart
  - Claustrophobia (fear of enclosed places)
  - Body piercing or tattoos
- Smartphone pain app rating*;
- A 15-minute MRI scan;
- Personal Health History (PHH)
- Complete questionnaires about general health and pain
  - Safety questionnaires for the TMS procedures.
  - PainDetect;
  - Short-form Montreal Pain Questionnaires (sfMPQ);
  - BDI
  - Pain Catastrophizing scale
  - PROMIS 57

* PainApp: participants will be instructed to use our smartphone-based app to report pain intensity (NRS, where 0 is no pain and 10 is worst imaginable pain), mobility (minimum, average, maximum), mood (NRS, where -10 is sad and +10 is happy), and medication use, collected twice daily from Visit 1 until the end of participation (~100 ratings).

MRI Scan:

Subjects will undergo MRI scanning at the Northwestern University, Department of Radiology Center for Translational Imaging (CTI). All procedures are standard in our laboratory and have been approved in multiple previous IRB protocols.

More specifically, we will conduct a MRI scan (Siemens Trio, 3T, 64-channel head coil) with both structural (T1 scan, 5 minutes) and rsfMRI (EPI scan, 8 minutes) protocols. No contrast will be used in the MRI.

The structural scan will allow us to use the built-in neuronavigation TMS system, for optimal localization of the stimulation sites. Resting-state fMRI will be used to identify the functional localization for indirect stimulation of the hippocampus. To do so, we will follow a well-established in-house processing pipeline, replicating the methods used in our previous experiments using this method [14–17]. Briefly, whole-brain seed-based correlation will be performed, using the left dorsal hippocampus as a seed region. This will allow us to identify, at a single-subject level, the exact parietal target that has maximal connectivity to the dorsal hippocampus. By stimulating this parietal target, modulation of the hippocampus connectivity can be achieved non-invasively [14,23] and with long-lasting effects in brain connectivity after three stimulation sessions [24].

In this same visit, participants will further complete questionnaires regarding pain ratings and the characteristics of their pain (see below for detail information).

Participants will be assigned to one of the six possible stimulation sequences and trained on our pain app (a smartphone-based tool used to rate pain and mood on NRS scales, as well as indicate rescue medication use, twice a day). They will be asked to use the pain app for the next 7-10 days prior to the first round of intervention and during all the study duration.

There will be 2 MRI visits: one at baseline (visit 1), the second MRI will depend on participants allocation: participants randomized to group 1 will have a second MRI at visit 6; and participants randomized to group 2 at visit 11.

- **Visit 2 – 11** (Approx Time: 1 hour)

Intervention visits: These visits will be scheduled ~1 week after the visit 1 measurements are done.

At visit 2, the stimulation protocol will start, and participants will receive a total of 10 sessions: 5 consecutive daily sessions of each stimulation round following the prior stimulation sequence order, interleaved by 2 weeks of wash out period. All subjects will undergo sessions of sham, and hippocampal-stimulation, in a crossover manner. As different stimulation conditions (hippocampal, M1 or sham) will be delivered in each of the two rounds of stimulation, participants will be told that stimulations can feel and sound different.

Before stimulation, the subjects will complete the following assessments:

- NRS for back pain

After each session, subjects will complete the following assessments:

- Side Effects Questionnaire for rTMS
- NRS for back pain
- At visits 6 and 11 participants will also complete the following questionnaires:
  - PainDetect;
  - Short-form Montreal Pain Questionnaires (sfMPQ);
  - BDI

Global impression of changeAfter the end of Round 1 or Round 2:

- MRI

Sources of materials

Research materials to be obtained from participants:
Urine specimens will be collected at the screening visit to check for illicit drug use. In addition, women of childbearing potential will be required to have a urine pregnancy test at screening visit ensure a negative result (testing required by our MR unit; these tests will be disposed of at the visit).

Research data collected from participants:

There are several types of data that we will be collecting: brain images; self-report questionnaire measures; and physical, psychological, and physiological parameters. In addition, clinical and demographic data will be obtained, including: complete information regarding descriptors of the participants' back pain (duration, frequency and magnitude of pain, etc) as well as a general medical history including surgical and treatment history, disability status, drinking and drug use, demographics, smoking status, height and weight. For all participants, the smartphone app will be used to monitor medication use, ratings of back pain intensity (NRS), mood and mobility, twice daily until the end of the study participation

Questionnaires used for assessing characteristics of cohorts:

- **Personal Health History (PHH):** This general questionnaire will assess demographic information (gender, age, marital/relationship status, race/ethnicity, and education), pain history (descriptions, diagnostic testing history, and treatment history), general health history (other medical/surgical history, concurrent medications, health behaviors, a general symptom

checklist, and health-care utilization), and work history. The entire questionnaire will be completed at the visit 1. Subjects will be asked about any changes to concurrent medications at subsequent visits. History and physical examination will be done to confirm diagnosis, inclusion and exclusion criteria and assess overall safety.

- **Vitals measurements**: blood pressure, heart rate, respiration rate, height and weight will be measured.

- **PainDETECT (PD-Q)**: A 12-item self-report instrument that assesses neuropathic pain properties and was originally developed in a sample of 8,000 low back pain suffers in Germany. The PD-Q demonstrates high sensitivity (80%) and specificity (85%) and has since been validated in other clinical pain populations. Although this instrument has not been validated in OA populations, it has been widely used in numerous OA studies[25].

- **Beck Depression Inventory, second version (BDI-II):** A 21-item self-report instrument for measuring the severity of depression in adults. It is well validated in pain populations and has been extensively used in pharmacological research[26].

- **Short-form Montreal Pain Questionnaires (sfMPQ):** A well-validated pain measure, which permits separation of sensory and affective components of pain, as well as a total pain score. It also includes a numeric/descriptor scale, a visual analog pain scale (VAS), and a body map to localize the pain[27]. This instrument is very well validated and often used in pharmacological research. However, its affective subscale is thought to be relatively rudimentary. It will be used to track development or continuation of pain, as well as post-surgical pain.

- **Numerical Rating Scale (NRS): is** an 11-point numerical rating scale used to measure pain intensity, where 0 corresponds to no pain and 10 indicates worst possible pain[28]. The timeframe in question is concerned with the average pain experienced at the moment, in the past 24hrs, or average over past week. This questionnaire has been extensively used across pain management studies.

- NIH PROMIS-57 Profile: This 57-item questionnaire contains brief scales for anxiety, depression, fatigue, pain interference, pain intensity, physical function, sleep disturbance, and the ability to participate in social roles. Each scale was created using PROMIS methodology and calibrated using item response theory.

- Pain Catastrophizing Scale (PCS): The PCS is a 13-item instrument derived from definitions of catastrophizing described in the literature as well as items from the catastrophizing subscale of the CSQ. The PCS instructions ask participants to reflect on past painful experiences, and to indicate the degree to which they experienced each of 13 thoughts or feelings when experiencing pain, on 5-point scales with the end points (0) not at all and (4) all the time. The PCS yields a total score and three subscale scores assessing rumination, magnification and helplessness. The PCS has been shown to have adequate to excellent internal consistency (coefficient alphas: total PCS = .87, rumination = .87, magnification = .66, and helplessness = .78).

- Global impression of change (PGIC): this questionnaire reflects a patient's belief about the efficacy of treatment. Although widely used in chronic pain clinical trials, PGIC's validity has not been formally assessed. PGIC is a 7 point scale depicting a patient's rating of overall improvement.

• **Description of smartphone PainApp:** All participants will also use a smartphone app to log their back-pain intensity, their mood, their mobility and medication use and other information that they may wish to report. The smartphone data are entered every day during the study and after termination of treatment until the final study visit. Smartphone entries are immediately transmitted through Wi-Fi to a secure web site, downloaded daily to assess compliance, and stored in a second secure server (we have been using such apps for about 6 months and they have been very effective).

Procedures	Visit 1	Visit 2,3,4 5,7,8,9,10	Visits 6 and 11
Informed consent process	X		
Inclusion/exclusion criteria	X		
Demographic survey and patient information criteria	X		
Pregnancy test (if applicable)[1]	X	X[1]	
Drug urine test	X		
Vitals measurements	X		
Personal Health History (PHH)	X		
General physical exam	X		
BDI	X		
MRI	X		X[2]
Pain Detect Questionnaire (Pdq)	X		X
Short-form Montreal Pain Questionnaires (sfMPQ)	X		X
Pain Catastrophizing Scale (PCS)	X		
NIH PROMIS-57 Profile	X		
Randomization	X		
rTMS stimulation		X	X
NRS before/after stimulation		X	X
NRS average pain			X
Adverse events questionnaire		X	X
PainApp (During all the study)[3]	X	X	X
Approximate visit duration	2-3 hrs	1-2 hrs	1-2 hrs

Table 1: Related Procedures and Study Schema. Visits 1 through 10 will be completed according to the presented schema. 1.There is no specific recommendation for or against pregnancy, however, since this study will be utilizing Repetitive TMS as a mode of intervention, we will take the conservative approach and exclude pregnancy. Female subjects of childbearing potential will be asked to take a pregnancy test. If the pregnancy test is positive, the subject may not enroll in the study. Pregnancy test will be repeated in visits 2 and 8 (every ~ 2 weeks).

2. Visit 6 and 11: These visits will be separated in two parts: part 1: last day of stimulation (stimulation + questionnaires) and part 2: MRI (at least 24hrs after part 1). For group1, only visit 6 will have 2 parts and for group 2 only visit 11 (see Figure 1 for details).
3. PainApp: participants will be instructed to use our smartphone-based app to report pain intensity (NRS, where 0 is no pain and 10 is worst imaginable pain), mobility (minimum, average, maximum), mood (NRS, where -10 is sad and +10 is happy), and medication use, collected twice daily from Visit 1 until the end of participation).

DATA AND SPECIMEN BANKING

Data will initially be entered onto case report forms and then into the Research Electronic Data Capture (REDCap) database. All questionnaires will be electronic (created or copied into REDCap) and completed by the participant via links sent to his/her email address. Once completed, the questionnaire data are stored in the REDCap database and cannot be altered by any team members. This process will be designed so that the system automatically sends the correct questionnaires at defined intervals and tracks participants over the follow-up, informing research staff either when participants have completed the battery or when they have gone outside the allotted time window and must be called. Thus, REDCap will aid in the promotion of scheduled and diligent contact between participants and the research team. All remaining data will be collected by the designated clinical manager as well as by the MRI research team. Scanning data will all be digital and is burned onto DVDs, sent to a Northwestern University archive system, and stored in the lab's secure servers. Likewise, data collected with our smartphone app will be digitally stored in the lab's secure server. Only subjects' participation identification numbers (PIDs) will be included in any of these materials; a master study list will be maintained by the lead clinical investigator (TJS). Access to this list will be limited to the site investigators, clinical coordinator, and other study personnel directly involved with data collection on an as needed basis. All the data will be collected specifically for this study and not in the course of usual clinical care. All non-digital data (e.g., consent forms) will be stored in a locked cabinet in a locked room. Any digital information will be pass-word protected and if any of this has identifying information on it, it will be encrypted.

Access to PHI:

All data collected will be linked to participants by their unique study participation identification numbers (PIDs), provided at the time of screening. A master study list linking participants' names to study identification numbers will be the only means of linking data to specific individuals. This list will be kept on an encrypted personal computer residing in the Apkarian lab, not connected to the internet, and with password protection. Only Apkarian and Schnitzer will have access to this file, and it will only be used in case of an unforeseen emergency need.

SHARING RESULTS WITH PARTICIPANTS

Screening laboratory tests may be shared with the participants and/or their physicians at their request. The results of the questionnaires and brain scans will not be provided to the participants.

STUDY TIMELINES

Participants may be involved for approximately 7 weeks; for a total of 11 visits. Each treatment period will consist of five consecutive days of stimulation sessions followed by two weeks wash

out period. It is anticipated that enrollment will require approximately 8 months. The primary analyses will be completed 6 months later.

INCLUSION AND EXCLUSION CRITERIA

Pre-screening of participants will occur by phone or email. We will discuss the study aims and objectives, the procedures that will need to be followed, and the risks and potential benefits with all individuals during pre-screening procedure. A written consent form will be provided to each subject prior to any procedures being carried out; this will be read by the potential subject and any and all questions answered by the coordinator and/or site investigator. Subject will sign two copies of the consent form; one will be given to the subject and one will be kept in the subject's file.

Inclusion Criteria:

- ≥ 6 months of back pain on a daily basis;
- male or female with no racial or ethnic restrictions;
- 18 to 75 years old;
- average back pain intensity > 4/10 at study entry;
- must be able to read, understand, and sign consent form;
- generally healthy.

Exclusion Criteria:

- back pain with fever, chills, rheumatoid arthritis, ankylosing spondylitis, acute vertebral fractures,
- history of tumor in the back;
- back surgery within the past 6 months;
- Chronic neurologic conditions, e.g., Parkinson's
- involvement in litigation regarding back pain;
- other severe medical diseases;
- pregnancy;
- positive urinary screen for any recreational drugs,
- opioids use;
- use of anticoagulants (low dose ASA allowed);
- history of gastric ulcer; renal insufficiency or congestive heart failure,
- contraindication to MRI,
- contraindication to TMS; including history of seizure/epilepsy*
- Any medical condition that in the investigator's judgment may prevent the individual from completing the study or put the individual at undue risk;
- In the judgment of the investigator, unable or unwilling to follow protocol and instructions;
- Diagnosis of major depression;
- Intra-axial implants (e.g. spinal cord stimulators or pumps)

* contraindication to TMS such as: history of seizures, unexplained loss of consciousness, any metal implants in the head, frequent or severe headaches or neck pain, any other electronic implanted medical devices such as pacemakers, defibrillators, or implant medication pump.

VULNERABLE POPULATIONS: NONE

PARTICIPANT POPULATION(S)

Accrual Number:	Category/Group: (Adults/Children	Consented: Maximum Number to be	Enrolled: Number to Complete

	Special/Vulnerable Populations)	Consented or Reviewed/Collected/Screened	the Study or Needed to Address the Research Question
Local	16	16	16
Study-wide	16	16	16
Total:	16	16	16

RECRUITMENT METHODS

Potential patients will be screened via a database maintained by one of the co—investigators (TJS), the registry is approved under the IRB (STU00007522 - Protocol title: Physical Medicine & Rehabilitation Registry). We will also extend recruitment through community and partnerships with medical institutions (Northwestern Medicine, Shirley Ryan AbilityLab), through online advertisement, and by flyer-based methods including ads.

Materials that will be used to recruit subjects will be uploaded in the IRB application, and only used once they have been approved. They include ads, brochures, and letters. Contact information on the fliers/ads and other subject facing recruitment materials will be updated as needed without IRB approval. No other content on the subject facing recruitment materials will be changed without IRB approval, only contact information.

COMPENSATION FOR PARTICIPATION IN RESEARCH ACTIVITIES

Participants will not be paid at the time of prescreening. For the screening visit, participants will receive $75 ($25 for questionnaires + $40 for the MRI) for travel and their involvement. For visits after the screening period (V2-V11) participant will receive $20/stimulation session; $100 dollars will be reloaded at the PNC card after each stimulation round (5 visits). Participants will receive $40 dollars for each MRI completed. Participants will receive $0.25 per eDiary entry recorded throughout the study, ratings are capped at a max of 2/day and as the study lasts approximately 7 weeks. In addition, participants will receive an extra $20 if complete all the study visits and bonus of $20 dollars if they complete more than 90% of the pain diary ratings (90% is approximately 90 rates). In all visits, participants can opt to receive a parking voucher. If a parking voucher is required for one of the Northwestern Parking garages, $6 will be deducted from total visit payment. Payment may be prorated based on visit completion. All compensation will be made using a Stored Value Card (VISA).

Visit	Number of Visits	Amount per visit	Total Amount	Payment Type
Screening/MRI completion	1	$75	$75	PNC card
V2-V11	10	$20	$200 + $20[1]	PNC card
Second MRI completion	1	$40	$40	PNC card
PainApp ratings	100	$0.25 dollar/response, 2 times per day maximum + $20[2]	$25 + $20[2]	PNC card

[1] Participants will receive an extra $20 if complete all the study visits, including 10 stimulation visits.
[2]If participants complete 90%of all pain diaries entries (around 90 entries) they will receive an additional $20 dollars at the of the study.

WITHDRAWAL OF PARTICIPANTS

Participants may be withdrawn from the study if they are not able to undergo brain MR imaging or if they do not provide regular pain data with the cellphone app. Participants will be notified that they will have to discontinue the study if those circumstances occur.
If a participant withdraws early, payment will be made for the portion of the research study that has been completed (prorated to the nearest 1-hour increment). Incomplete data sets obtained from participants (due to early withdrawal) will be excluded from the primary analysis and included in an exploratory full dataset analysis.

RISKS TO PARTICIPANTS

Taking part in this study may involve the following risks:

The most common side effects of rTMS can include mild headaches or discomfort at the stimulation site. This occurs in approximately 5% of subjects. The subject is allowed to stop the stimulation at any time if they feel uncomfortable. These effects generally wear off shortly after the session and can be treated via over-the-counter analgesics. If subjects experience discomfort at a stimulation location, research staff will attempt to move the stimulator to a location that minimizes this discomfort. Research staff will be in constant contact with the subject during the rTMS procedure and will discontinue the protocol if discomfort cannot be successfully reduced. Vital signs will be collected and used to exclude subjects from rTMS if outside of normal established ranges (see above). With the permission of the subject, the primary care physician will be contacted by the research team to arrange follow-up care if vital signs are outside of the normal range.

Although extremely rare, undergoing rTMS may induce a seizure. The risk of seizure due to rTMS is extremely rare with the rTMS procedures that will be used under this protocol. The screening procedures and rTMS stimulation protocol used here is in accordance with recommendations by the safety of TMS consensus group and by the international workshop on the safety of repetitive TMS, and the proposed rTMS procedures are classified as very low in risk based on these recommendations. The risk of seizure for our rTMS parameters among individuals meeting our safety requirements (including no history of seizure/epilepsy, among other exclusionary criteria) is quantified in two publications: Rossi et al. (2009)[18] and Oberman et al. (2011)[22]. Rossi et al. Identified one instance of seizure among all studies conducted from 1998-2008 among subjects with no history of seizure meeting our inclusion/exclusion criteria. There were additional instances of seizure reported among subjects who would be excluded from our studies because of psychiatric diagnoses, current use of anti-psychotic drugs, and neurological diagnosis, all of which are exclusionary for our studies. The risk estimate quantified from Rossi et al., 2009, for subjects meeting our criteria is 0.01% likelihood of seizure during a rTMS session. Oberman, 2011, reviewed studies using the same inclusion/exclusion criteria as in our studies and report a risk of 0.02% likelihood of seizure during a rTMS session. The risk of seizure for an individual with no seizure history and meeting our other inclusion/exclusion criteria is therefore approximately 0.01-0.02% (~1 to 2 in 10,000).

Despite the very low risk of seizure for these procedures, trained clinical staff (nurse, doctor, nurse practitioner or a physician assistant) will be present for all rTMS sessions. Trained clinical

staff will be available for all sessions, however they will stay in an adjacent room observing with no direct unnecessary contact with the subjects. This is a mechanism study and only subjects will be blinded to the stimulation sequence. This will not compromise blinding. The clinical staff will monitor subjects for any signs of seizure, especially tonic-clonic muscle contractions associated with grand mal seizure. In the case of a seizure, rTMS procedures will be immediately terminated and an emergency response unit (911) will be called. The trained clinical staff will perform standard medical intervention for seizure. We will follow standard in-house safety protocol required by CTI. In the rare event that a seizure the attending neurologist collaborating with the study - Dr. Vanhaerents will be notified as soon as possible, and subjects will be released to emergency medical care upon their arrival.

With MRI, there is risk of claustrophobia and anxiety involved with the scanning procedure, which involves the potentially uncomfortable experience of lying in a relatively confined space with minimal head and body movements for up to 15 minutes at a time. In this time period, their pain (if they have any) may become worse. Over the last 20 years of doing brain scans in various populations (healthy and not), the main limiting factor has been claustrophobia. Participants also may feel anxious in the scanner and simply cannot tolerate it.
With regard to the questionnaires, although the majority of participants will find these to be harmless, mundane, or possibly interesting, there is always a possibility that some of the questions may be sensitive in nature and may make them uncomfortable (particularly those asking about mood or personality). All questionnaires have the option of being marked as “will not answer”. Any task that subjects are not comfortable with will be skipped. These tasks are administered by trained personnel and they are well aware of such potential limitations and take full care not to expose volunteers to undoable tasks.

There is no known fetal risk from MRI scanning during pregnancy; however, the absolute safety has not yet been established. Therefore, any patient who is pregnant or states that there is a possibility of being pregnant will not be excluded from the study.

POTENTIAL BENEFITS TO PARTICIPANTS

We cannot promise any benefits; however, possible benefits include a decrease in pain as a result of the stimulation sessions. We are not able to estimate at this time the probability, magnitude or duration of benefit. We hope to define these parameters with the results of this study.

DATA MANAGEMENT AND CONFIDENTIALITY

Data will initially be entered onto case report forms and then into the Research Electronic Data Capture (REDCap) database. All questionnaires will be electronic (created or copied into REDCap) and completed by the participant via links sent to his/her email address. Once completed, the questionnaire data are stored in the REDCap database and cannot be altered by any team members. This process will be designed so that the system automatically sends the correct questionnaires at defined intervals and tracks participants over the follow-up, informing research staff either when participants have completed the battery or when they have gone outside the allotted time window and must be called. Thus, REDCap will aid in the promotion of scheduled and diligent contact between participants and the research team. All remaining data will be collected by the designated clinical manager as well as by the MRI research team. Scanning data will all be digital and is burned onto DVDs, sent to a Northwestern University archive system, and stored in the lab’s secure servers. Likewise, data collected with our smartphone app will be digitally stored in the lab’s secure server. Only subjects’ participation

identification numbers (PIDs) will be included in any of these materials; a master study list will be maintained by the lead clinical investigator (TJS). Access to this list will be limited to the site investigators, clinical coordinator, and other study personnel directly involved with data collection on an as needed basis. All the data will be collected specifically for this study and not in the course of usual clinical care. All non-digital data (e.g., consent forms) will be stored in a locked cabinet in a locked room. Any digital information will be pass-word protected and if any of this has identifying information on it, it will be encrypted.

Data Analysis Plan

MRI data will be analyzed using the FSL software library [30]. Briefly, structural data will be skull-stripped and normalized to MNI space through nonlinear transformation. Functional data will be motion corrected and smoothed with a 4 mm smoothing kernel. Data will be further denoised by performing motion-censoring and regressing out the motion parameters. Finally, data will be band-pass filtered (0.01 to 0.1 Hz). Functional connectivity analyses will be carried on by performing Pearson correlations between the BOLD time series of a hippocampal seed and all other voxels in the brain. The maximal statistically significant cluster near a predetermined coordinate in the parietal cortex (see Wang et al. 2014) will be extracted, spatially warped to the subject native space, and fed into the TMS neuronavigation system for stimulation.
Statistical analyses will be performed using the software R. We use repeated-measures within-subject analysis of variance for dependent variables 1) change in painApp immediately after rTMS relative to baseline, and 2) for change in painApp in the long term (average over the second week after rTMS) relative to baseline, with independent factors being hippocampus-rTMS and sham-rTMS; with Bonferroni post-hoc comparisons. If the ANOVAs are significant and post-hoc comparisons indicate superiority of hippocampus-rTMS, we declare that the approach is a clinically important means of pain control in CBP, and newer larger studies should be launched.

Power Calculation

This study aims to collect preliminary data in humans to test whether a manipulation of the hippocampal network can lead to changes in pain experience in CBP participants. With this in mind, we will aim for a final sample size of 12 subjects. Due to possible dropouts over the course of the study, we will recruit a total of 16 subjects. If this study shows indication that the hippocampal stimulation leads to higher connectivity increase across series of hippocampal networks that modulates pain, the results of this study will be used to perform a power calculation in order to perform a future study aiming to treat chronic back pain.

PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF PARTICIPANTS

The primary protection will be careful recruitment, thereby limiting enrollment only to eligible subjects, i.e., subjects meeting all inclusion and exclusion criteria.

MR Imaging

Individuals who cannot tolerate the confinement of an MRI scanner and those who may not be able to be scanned because of implanted metal devices will be excluded. Claustrophobia is the main limiting factor; we attempt to identify people at risk by having people lie in the simulation scanner (a fake scanner made to look and feel like the real one) to assess their comfort levels. There is a standard checklist of additional exclusionary items for MR scanning (e.g., implanted devices, exposure to metallic fragments at work, etc) that will be utilized prior to entering participants into the study and again prior to each imaging session. Personnel continuously query the subject in the scanner as to their overall well-being during scans and will discontinue the scan

and relieve the subject from the discomfort at any time requested. It is possible that the anatomical scans may uncover a brain abnormality of which the participant was not aware. In such cases, the subject is removed from the study and given appropriate medical advice (TJS); his/her scans are sent to a radiologist for an opinion and this person then consults with TJS. The likelihood of this happening is low (less than 1%). Over the last 20 years of doing brain scans in various populations (healthy and not), participants often are surprised at how anxious they feel in the scanner and simply cannot tolerate it. Otherwise, subjects are usually enthusiastic in participating in trials that may lead to new discoveries that either pertain to their conditions or help other people.

TMS

Individuals who cannot tolerate TMS stimulation or those who may not receive stimulation will be excluded. To minimize risk and protect participants, a trained clinical staff will be present for all the rTMS sessions (a trained clinical staff will also be present on “sham” sessions, even though in these sessions the intensity of stimulation is adjusted to a low value that cannot influence the brain). Study staff personnel continuously query the subject regarding their overall well-being during the stimulation protocols and will discontinue and relieve the subject from the discomfort at any time requested.

Questionnaire Risks

To deal with the possibility that some questions may be sensitive in nature or make people feel uncomfortable, individuals will be told that they need not complete any items of entire questionnaires if they feel that doing so will cause discomfort. Because we are measuring depression, anxiety, and other mental health constructs in these questionnaires, Dr. Griffith, a licensed clinical psychologist, will be available to consult about any concerns that patients have about their mental health, including referrals to appropriate providers. All such participants will be given a list of referral sources in case they wish to seek mental healthcare, and participants will be invited to contact the research team with any questions about getting connected with appropriate healthcare.

PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS

Privacy and confidentiality will be maintained using allocation numbers (also called participant IDs, PIDS) throughout the study with the master study list being maintained by the PI and study coordinator with availability limited to those study personnel who have a documented need for this information. All electronic information will be pass-word protected and stored on a secure server; when necessary, it will also be encrypted for extra protection.

To deal with the possibility that some questions may be sensitive in nature or make people feel uncomfortable, individuals will be told that they need not complete any items of entire questionnaires if they feel that doing so will cause discomfort. Because we are measuring depression, anxiety, and other mental health constructs in these questionnaires, Dr. Griffith, a licensed clinical psychologist, will be available to consult about any concerns that patients have about their mental health, including referrals to appropriate providers. All such participants will be given a list of referral sources in case they wish to seek mental healthcare, and participants will be invited to contact the research team with any questions about getting connected with appropriate healthcare.

COMPENSATION FOR RESEARCH-RELATED INJURY

If a subject is injured as a result of this study (medications, or procedures), they should seek medical treatment through their primary care physician or treatment center of choice. They will be instructed during the consent process to promptly tell the study doctor about any illness or injury. The hospital [university, researchers] will not pay for medical care required because of a bad outcome resulting from participation in this research study.

ECONOMIC BURDEN TO PARTICIPANTS

Participants will not be responsible for any study-related costs because of participation in the research.

CONSENT PROCESS

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. We will be obtaining informed consent for all subjects in this study. We do not plan to enroll non-English speaking subjects, cognitive impaired individuals, individuals under 18 years of age, and or adults who are unable to consent.

<u>The following outlines the informed consent process:</u>

After passing the pre-screening over the phone, the participant will be scheduled for a screening visit. If possible, a copy of the IRB-approved consent form will be emailed or mailed to the subject prior to the scheduled visit.

The consent process will take place in Abbott Hall on the 10th floor clinical research exam space in a private exam room or in the CTI in a private room. The consent form will be explained to the participant (the participant will read along with staff): each section of the form will be discussed, taking time to highlight the purpose of the study, procedures, risks, confidentiality measures taken to protect the participant, and how to revoke/withdraw consent, if desired, and to answer any questions the participate may have. If staff cannot answer the question or if the participant has concerns to discuss, the study physician or PI will be contacted to speak to the participant. Subjects will be given as much time as they need to make their decision whether or not to participate. There will be a waiting period available to the participant; they will have an opportunity to take the consent document home to discuss with family, friends, and/or their physician prior to signing the document. Once the document is signed, the subject will sign and date two copies. One copy to take home and one copy to keep with the subject's source documents. The consent process will also be documented in the subject's source documents.

All participants will be re-consented should a new ICF be approved by the IRB with updated information. In cases where participants may need to be notified of new information before an ICF is approved by the IRB, subjects will be notified by phone about updated information.

This study will follow SOP: Informed Consent Process for Research (HRP-090) as well as "SOP: Written Documentation of Consent (HRP-091)."

NON-ENGLISH-SPEAKING PARTICIPANTS

Only English-speaking participants will be enrolled.

PROTECTED HEALTH INFORMATION (PHI AND HIPAA)

We are committed to respect participant privacy and to keep personal information confidential. When choosing to take part in this study, participants are giving us the permission to use their PHI that includes health information in their medical records and information that can identify them. For example, PHI may include name, address, phone number or social security number. Health information that we may collect and use for this research includes:

- Results of physical examinations
- Medical history including back pain history and family history of back pain
- Lab tests, or certain health information indicating or relating to a particular condition as well as information collected by cellphone apps
- Records about study medication or drugs
- Records about MRI scans
- Substance abuse information: current recreational drug use or history of alcohol or drug abuse

The following groups of people may give the researchers information about research participants: All current and previous health care providers, including but not limited to the NMH. Once we have the health information listed above, we may share some of this information with the following people. Please note that any research information shared with people outside of NU and its clinical partners (or affiliates) will not contain subject's name, address, telephone or social security number or any other direct personal identifier unless disclosure of the direct identifier is required by law [except that such information may be viewed by the Study sponsor and its partners or contractors at the PI's office]

- Authorized members of the NU workforce, who may need to see information, such as administrative staff members from the Office for Research, Office for Research Integrity and members of the Institutional Review Board (a committee which is responsible for the ethical oversight of the study),
- Clinical affiliates, including but not limited the NMH. Individuals' participation in this clinical trial will be tracked in an electronic database and may be seen by investigators running other trials and by other healthcare providers having access to this database.
- Other University research centers and University contractors who are also working on the study,

The informed consent document will include a HIPAA authorization as well.
The results of this study may also be used for teaching, publications, or presentation at scientific meetings. However, the individual's name and personal information will not be used.

QUALIFICATIONS TO CONDUCT RESEARCH AND RESOURCES AVAILABLE

Northwestern University, primarily through the Feinberg School of Medicine, is one of the country's premier centers in education, research, and clinical services. Interaction between scientists is supported and encouraged. The scientific environment is more than adequate to contribute to the success of the proposed research.

Apkarian's Lab center: The lab has a human and animal component of ~1800 square feet. The human brain-imaging lab has 3 post-doctoral fellows, PhD and undergraduate students.

The brain imaging data processing center of the lab was recently relocated at Northwestern University Data Center Facilities' secure datacenter located in Evanston Campus, and is accessed via a remote interface. All necessary software for analysis of neuroimaging and behavioral data is available.
Dr. Schnitzer has dedicated research space with 3 dedicated examination rooms, a phlebotomy room and clinical laboratory and 1400 square feet of office spaces for research staff. All clinical equipment required is available.
Laboratory for Human Neuroscience (LHN): The laboratory Dr. Voss occupies ~2,400 ft2. There are three testing enclosures outfitted for cognitive neuroscience experiments with human subjects. The laboratory maintains a dedicated MagVenture X100 MRI-guided TMS system and a variety of physiological monitoring devices and electrical stimulus generators. Dr. Voss's laboratory has easy access to all research spaces and is a Co-Investigator on this project.
Center for Translational Imaging (CTI): Human imaging Human brain imaging is done Center for Translational Imaging (CTI), a core facility of Northwestern University. There are two 3.0 T MRI scanners, dedicated for research and shared between 15 NIH funded research groups, having led to >100 publications. We have access to the MRI facilities for the next 5 years. CTI is managed by the Radiology Department and is fully staffed and equipped. Besides that, the LHN maintains a TMS system that is identical to the system housed in the CTI.
Research staff have all completed CITI training and have training in human subject's protection.

All personnel will be fully informed and trained regarding the protocol and follow the research clinic's SOPs for undertaking clinical studies. For rTMS, research staff has completed at least 20-hours of supervised hands-on experience operating the machine and interacting with participants. rTMS training is provided by Laboratory for Human Neuroscience.

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