Latent Aging Mechanisms in Pain and Sleep (LAMPS)

ClinicalTrials.gov Identifier: NCT04683640

Date: 5/10/2022

1. Project Title

Sleep, Pain, and Aging: Potential Underlying Mechanisms (**L**atent **A**ging **M**echanisms in **P**ain and **S**leep — **LAMPS** Study)

2. Investigators:

Yenisel Cruz-Almeida, PhD (PI)
Soamy Montesino Goicolea, MD (PI Proxy)
Pedro Antonio Valdes Hernandez, PhD (Co-I)
Eric Porges, PhD (Co-I)
Zhiguang Huo, PhD (Co-I)
Olga Nin, MD (Co-I)
Cameron Smith, MD-PhD (Co-I)

3. Abstract:

Chronic pain is a serious public health problem peaking at older age depending on the pain condition [1]. Similarly, the capacity to sleep properly changes with age with nearly half of older adults complaining of difficulty sleeping [2][3]. Although the bidirectional link between sleep and pain is widely established, the common underlying neurobiological mechanisms have yet to be fully elucidated, especially in aging. As currently available sleep and chronic pain therapies are only partially effective, novel treatment approaches are urgently needed. Given the potential mechanistic role of GABA in both conditions, based on our preliminary data and the availability of GABA supplements over the counter, the present proposal will determine the effect of oral GABA administration in sleep quality and pain in middle to older aged adults with chronic pain and sleep disorders as well as to characterize the potential neurobiological mechanisms involved in both conditions. Results from the present investigation using a parallel, double-blinded, placebo-controlled study will provide novel and the preliminary information needed for future translational pain and sleep research.

4. Background:

Chronic pain is a serious public health problem affecting all age groups peaking at older ages depending of the pain condition [1]. Similarly, the capacity to sleep properly changes with age with nearly half of older adults complaining of difficulty sleeping, changes which start around middle age [2][3]. Although the bidirectional link between sleep and pain is widely established, the common underlying neurobiological mechanisms have yet to be fully elucidated, especially in aging. As currently available sleep and chronic pain therapies are only partially effective, novel treatment approaches targeting shared potential mechanisms underlying both conditions simultaneously are urgently needed.

A shared mechanism linking poor sleep and chronic pain in aging is GABA deficiency. Gamma-Aminobutyric Acid or γ-aminobutyric acid (GABA) is the most important inhibitory neurotransmitter of the central nervous system (CNS). GABA has a broad range of effects on the body with lower levels of GABA being implicated in the modulation of stress, mood, sleep and pain [4][5][6]. Specifically, previous studies have shown negative associations between brain GABA concentrations with sleep disorders

and chronic pain independently (see Figure 1 for model) [7][8][10][11][12][13][14]. Our preliminary data suggest that 1) brain GABA concentrations are lowest in older adults that experience chronic pain using single-voxel proton magnetic spectroscopy (1H-MRS), and 2) those with the worse chronic pain reports have the worse self-reported sleep quality.

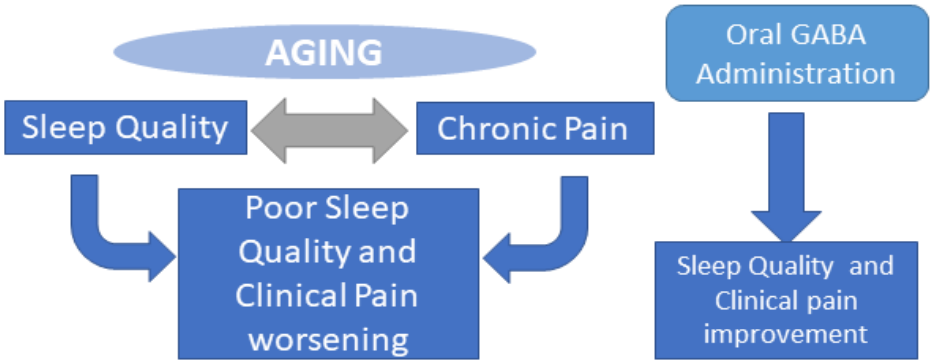


Figure 1. Mechanistic Working Model

Specific Aims:

Our study aims to examine associations between sleep and pain in middle to older aged individuals in two separate phases. These phases are independent from each other, although interested individuals may take part in one or both of the phases if they wish and qualify.

In the **first phase** of the study, middle to older aged individuals (n=100) and (n=50) younger controls, will provide 4 weeks of self-reported sleep and pain measures (i.e., validated sleep and pain questionnaires) as well as objective measures of sleep at home (i.e., by wearing a ring).

Specific Aim 1: To determine the associations between pain and sleep quality in middle to older aged adults. We will assess self-reported and objective sleep quality and a standardized, validated self-reported pain battery to community-dwelling older adults. Based on the literature, we hypothesize (**H1a)** that self-reported and objective sleep measures will significantly predict subsequent self-reported pain measures. We also hypothesize (**H1b)** that objective sleep quality measures will be better predictors of self-reported pain over the study period.

During the **second phase**, we will enroll a subset of middle to older aged adults with poor sleep and chronic pain who will self-administer oral GABA or placebo (P) over four weeks using a randomized, parallel group design (n=28). Before and after the intervention, participants will undergo clinical and experimental pain, as well as self-reported and objective sleep assessments. Proposed mechanisms will be evaluated using Magnetic Resonance Spectroscopy (MRS) for brain GABA, and HPLC for plasma GABA concentrations.

Specific Aim 2: To determine the effect of oral GABA administration on sleep quality as well as clinical and experimental pain in middle to older aged adults with poor sleep quality and severe pain. We will assess self-reported sleep and a standardized, multi-modal experimental pain battery measures. Informed by our pilot data, we hypothesize that compared to P, GABA treatment will result in significant improvements in: **H2a**) self-reported sleep quality; **H2b**) self-reported pain intensity **H2c**); objective sleep measures derived from OURA ring, and **H2d**) experimental pain sensitivity.

Specific Aim 3: To characterize the neurobiological mechanisms contributing to the interindividual variability in both sleep restoration and pain relief. Based on our preliminary data, we hypothesize that compared to P, GABA administration will result in significant: **H3a)** increases in brain GABA levels; and **H3b)** increases in plasma GABA levels. Further, **H3c)** increases in GABA concentrations will be significantly associated with improvements in sleep quality and pain.

Each phase of our study will advance our understanding of the interaction between sleep and pain in aging. The comprehensive evaluation of self-reported and objective sleep measures are highly relevant to function in the home and community, and will thus contribute to the ecological validity of our study.

5. Research Plan:

Our study aims to examine associations between sleep and pain in middle to older aged individuals in two separate phases. These phases are independent from each other, although interested individuals may take part in one or both of the phases if they wish and qualify. To reduce participant burden, portions of the study (including the ICF) may be conducted remotely via phone calls, UF Zoom, and/or online (REDCap).

First Phase of the Study

5.1. Participants, Recruitment and Compensation. We propose to enroll and screen 100 older adults over 45 years of age who up to 70% are expected to experience musculoskeletal pain and 50 younger controls between 18 and 30 years of age. All study visits during Phase 1 will be conducted via UF Zoom. Potential participants will be asked about subjective musculoskeletal complaints in the neck, shoulders, hands, lower back, knees and feet during the preceding 12 months and 7 days. We will attempt to recruit equivalent numbers of males and females and include minority adults. Recruitment of participants will also be accomplished using newspaper and a flyer that will be distributed electronically. We will also contact individuals in various IRB-approved registries.

Interested individuals will call our laboratory to learn about the study and complete a telephone or UF Zoom screening to establish preliminary eligibility. Participants will be compensated $50 once the study is completed and the ring is received by the study staff.

Study Exclusions: 1) ; history of alcohol/drug abuse in the past; 2) known intra-cerebral pathology or epilepsy; 3) significant cognitive impairment as evidenced by the TICS; 4) hospitalizations for mental health reasons in the past year; 5) chronic/current use of narcotic medications; and 6) inability to provide consent for study participation. If participants are excluded because of a TICS score < 30, the PI will attempt to contact the participants by phone and if unsuccessful by mail to explain that we are unable to include them at this time because their score(s) on a thinking/memory test, fell below the level we needed for eligible participants.The PI will also explain there can be many reasons why they did not reach the score level we needed, including difficulties with hearing, visual acuity, and lack of sleep. However, based on this score, they could also be experiencing other thinking, memory, and problem-solving changes that they might wish to discuss with their primary care provider. The PI will explain that this should not be a source of concern or alarm. However, we recommend that they share this information with their primary care provider. If the participant or their physician have any questions they are also welcome to contact the study PI for more information.

Initial Phone/Remote Pre-Screening. Interested individuals will call in using provided phone number and one of the study team members will complete a telephone interview. This will provide the individuals information about the study and if they are interested a pre-screening will be conducted. After the phone pre-screening, if participants are eligible and still interested in participation, we will send them the link to provide an electronic consent. Participants will be given the opportunity to read the consent on their own or share with others and we will reschedule a time to perform the electronic consenting process using REDCAP via UF Zoom. Once consent is obtained, the study team will either mail the participant the study binder with the questionnaires and the ring, as well as return-labels and mailing materials, or will

mail just the ring and administer the questionnaires via REDCap. At this time, we will also schedule the first visit within a week.

Baseline Remote Visit. In a UF Zoom visit within a week of consent, participants will be walked through the use of the ring, in particular, issues related to proper fit (i.e., which finger is a better fit), application and when/how to charge it. Traditional self-report measures of sleep cannot capture real-time data under naturalistic conditions or measure fluctuations on a daily or hourly basis. Data collection on the ring offers several advantages including the capability of long-term continuous data collection, ecological validity, and cost-effectiveness. Sleep quality will be captured each day throughout 30 days. Data will be downloaded remotely during the study. Participants will start wearing the device during this remote visit, and their proficiency and use will be ascertained during weekly check-in remote visits.

We will then go thru the following baseline sleep and pain questionnaires that was mailed to them in the study binder via Zoom:

Self-Reported Sleep quality will be assessed with the Pittsburgh Sleep Quality Index (PSQI) [39] and PSQI total score will be our primary sleep outcome measure to compare to the sleep quality measured by the ring. Secondary sleep measures include Berlin Questionnaire[40], Epworth Sleepiness Scale[41], PROMIS-Sleep Related Impairment Short Form 8a[47], and FOSQ-10: A Short Version of the Functional Outcomes of Sleep Questionnaire [48].

Self-Reported Pain will be assessed according to location, overall pain severity, and pain interference with daily activities using our pain history. Self-reported pain intensity will be our primary outcome measure for specific aim 1. We will also administer the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)[31] a reliable, well-validated measure of lower extremity pain and function in aging, the Owestry Low Back Pain Disability questionnaire and the NIH Low Back Pain Minimal Dataset as secondary outcomes to characterize sleep with self-reported knee/back pain and physical function. Pain-DETECT will be used to assess the degree of neuropathic pain experienced by our participants. Participants will also be issued a brief pain questionnaire as it relates to the ongoing COVID-19 pandemic to assess how it has affected their pain and access to care for it.

At the end of this visit, we will explain how to fill out the sleep diary, which provides an assessment of habitual bedtimes and waketimes in a single administration questionnaire format. We will also schedule 2 additional brief check-in remote visits and a final visit to be completed in approximately 30 days. The baseline remote visit will last no longer than 3 hours and we will take breaks as needed and will be held over UF Zoom.

Weekly Check-in Remote Visits. During these brief visits completed under 30 minutes, we will confirm completion of sleep diaries where participants provide an assessment of habitual bedtimes and waketimes in a single questionnaire. We will also ask one question regarding rating of pain, mood and sleep during the past 7 days, and we will confirm the correct use of the ring.

If you are a female under the age of 62 years old, we will ask you to self-report whether you are currently pregnant during the online visits.

Final Remote Visit. During this UF Zoom visit, the questionnaires from the baseline visit will be readministered and the visit will not last longer than 3 hours taking breaks as needed. We will also provide instructions for returning the ring and charger via mail including how the compensation will be processed once the ring is received. We will also provide the participant with their ring data if they want to.

Second Phase of the Study

We propose a double-blinded, randomized parallel group study that will randomize older adults with musculoskeletal pain and poor sleep quality to oral self-administration of either GABA (two 250mg capsules for a total of 500mg daily) or Placebo during four weeks. Our study design was guided by recommendations by the IMMPACT group for clinical pain trials [23][24][25][26] see table 1. After initial screening, eligible participants will undergo two 2.5-hour baseline sessions (health, sensory, and neuroimaging) for the collection of clinical information, QST, and brain imaging data. During the entire study, participants will wear a OURA ring to objectively measure sleep quality. During the intervention, participants will receive a phone call once a week for an assessment of adverse effects and compliance. During the last week of the intervention period, two assessment sessions will follow, these will be identical to the baseline sessions. (Figure 5.)

To reduce participant burden and exposure risk to COVID-19, the ICF may be conducted remotely via phone calls, UF Zoom and/or online (REDCap). A copy of the signed ICF will be provided to the participant.

Participants: Older adults over 45 years of age who have a smartphone and have experienced pain of at least moderate intensity (>5/10 pain intensity ratings) on more days than not during the past three months, and who also reported poor sleep quality (>5 PSQI scores) will be considered for participation. Community-based recruitment methods established in Dr. Cruz-Almeida's lab will be utilized.

Exclusion criteria will align with study and safety requirements broadly related to GABA administration, pain and MRI : 1) serious psychiatric conditions (e.g., schizophrenia, major depression, bipolar disorder;

Table 1. Study measures consistent with core outcome domains recommended by IMMPACT- www.immpact.org

IMMPACT Core Outcome Domain	Proposed Study Measures
Pain	Verbal Descriptor Scale (VDS) WOMAC-Pain
Physical functioning	WOMAC-Physical Function
Socio-emotional functioning	BDI-II PANAS
Sleep	Pittsburgh Sleep Quality Index Berlin Questionnaire Epworth Sleepiness Scale Oura Ring Sleep Diary
Improvement and satisfaction with treatment	Multidimensional Patient Impression of Change

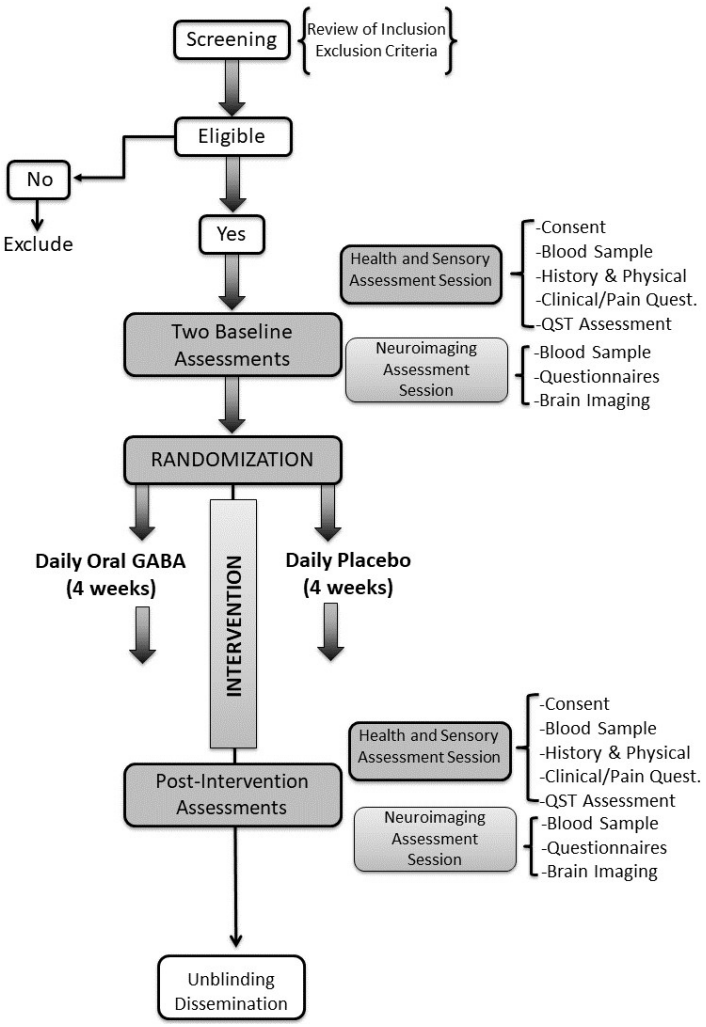
Symptoms and adverse events	Passive capture of spontaneously reported adverse events and symptoms, with the use of open-ended prompts
Disposition	Detailed information regarding participant recruitment and progress throughout the trial Self-reported evaluation of blinding

2) history of alcohol/drug abuse; 3) Alzheimer, Parkinson, Epilepsy and other known intra-cerebral pathology and neurological conditions; 4) significant cognitive impairment as evidenced by the Modified Mini-Mental State Examination [3MS] score ≤ 77; 5) hospitalizations for mental health reasons in the past year; 6) chronic/current use of narcotic medications; 7) serious systemic (uncontrolled diabetes self-reported HA1C>7), (uncontrolled hypertension > 155/90 mm Hg) and rheumatic disorders (i.e., rheumatoid arthritis, systemic lupus erythematosus, fibromyalgia, HIV); 8) arterial hypotension; 9) digestive tract diseases; 10) major medical surgery in the past two months, history of brain surgery or any serious brain condition like aneurysm, stroke, or seizures; 11) excessive anxiety regarding protocol procedures; 12) Inability to consent for study participation; 13) Ingestion of sleep medications including those with zolpidem (Ambien and others) and eszopiclone (Lunesta and others); 14) Neuropathic pain medications including anticonvulsants and antidepressants; 15) Allergies or sensitivity to GABA or its ingredients cellulose, gelatin (capsule), magnesium silicate, vegetable stearate and silica or to the placebo or its ingredients: calcium laurate, hypromellose capsule, magnesium (citrate), microcrystalline cellulose; 16) currently taking barbiturate and benzodiazepine and baclofen; 17) MRI contraindications including large pieces of metal in the body/face/neck and claustrophobia; 18) current cancer diagnosis unless determined no evidence of disease or in remission for at least two years, and 19) pregnancy

Initial screening: Interested individuals will call in using the provided phone number and after the phone consent that provides the individual information about the study and if they are interested, a pre-screening will be conducted. This screening procedure will include two questions regarding general body pain, two questions regarding back pain and seven questions regarding sleep quality in the past month. Will also assess age, gender, and additional health history information, as well as a questionnaire to assess MRI eligibility. After the phone pre-screening, if participants are eligible and still interested in participation, the baseline orientation visit will be scheduled. **Baseline Health & Sensory Assessment Session**: After receipt the signed copy of the informed consent previously obtained using REDCap, participants will provide a fasting blood sample to evaluate standard clinical parameters (Comprehensive Metabolic Panel (CMP-14) Blood Test) and a Urine sample to measure urine specific gravity, which will be reviewed by a physician to determine study continuation. For women under the age of 62, pregnancy tests will also be conducted.This session will take place in the mornings to accommodate for fasting and to control for circadian fluctuations.

*Physical examination***.** Height and weight will be measured as well as vital signs. Participants will complete a thorough Medical and Pain History Questionnaire, including a review of bodily systems assessing the reported duration of their pain, comorbid conditions, and current medication use.

Figure 5. Study Procedures



Sleep quality will be assessed with the Pittsburgh Sleep Quality Index (PSQI) [39] and PSQI total score will be our primary sleep outcome measure. Secondary sleep measures include Berlin Questionnaire[40], Epworth Sleepiness Scale[41], PROMIS-Sleep Related Impairment Short Form 8a[47], and FOSQ-10: A Short Version of the Functional Outcomes of Sleep Questionnaire [48].

Clinical pain will be assessed according to location, overall pain severity, and pain interference with daily activities using our pain history and the short form of the brief pain inventory. These measurements will encompass the key dimensions for pain assessment as recommended by the American Geriatrics Society[27] and according to the pain taxonomy by the Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks and the American Pain Society group (AAPT)[28][29]. Self-reported pain intensity will be our primary clinical outcome measure to characterize treatment effects in pain using the Verbal Descriptor Scale. We will also administer the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC),[31] a reliable, well-validated measure of lower extremity pain and function in aging, the Owestry Low Back Pain Disability questionnaire and the NIH Low Back Pain Minimal Dataset as secondary outcomes to characterize oral GABA effects in self-reported knee/back pain and physical function. Pain-DETECT will be used to assess the degree of neuropathic pain experienced by our participants. Short-form McGill Pain Questionnaire (SF-MPQ-2) to rate the extent to which they experienced each of 22 pain descriptors in the past week using an 11-point numeric rating scale (0 = “none” to 10 = “worst possible”). The West Haven-Yale Multidimensional Pain Inventory (WHY-MPI) questionnaire will also be issued to assess the participant’s chronic pain experience through several key dimensions, including the extent of the psychological and behavioral aspects of how the participant’s pain experience is impacted and communicated to others through their daily routines[53]. ***Emotional function*** will be assessed using The Beck Depression Inventory, 2nd Edition[34] is a widely used depression scale that assesses affective (e.g., sadness, loss of interest), cognitive (e.g., worthlessness, guilty feelings), and somatic (e.g., changes in sleep, tiredness or fatigue) symptoms common amongst depressed individuals. It contains 21 self-report items assessing the frequency and severity of depressive symptoms over the previous two weeks. Since item # 9 from the Beck Depression Inventory refers to suicidality, the experimenter will, before the end of the test session, review the participant's response to this item, and if the participant has chosen response option 2 = “I would like to kill myself “or 3 = “I would kill myself if I had the chance”, the experimenter will contact the PIs immediately and the PIs or their designee will contact Dr. Ronald Cohen at the University of Florida Psychology Clinic (352-265-0294)

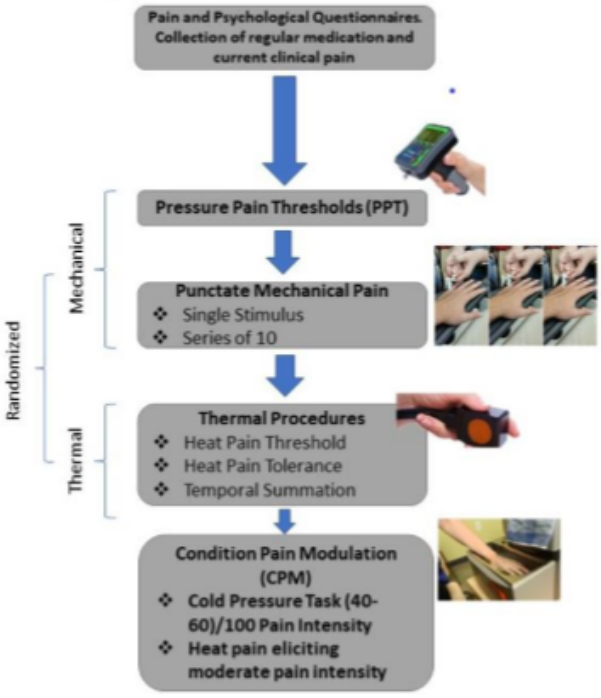
who will make recommendations. In the unexpected event that the clinic personnel are not available, the Alachua County Crisis Center will be contacted. The same procedure will be implemented for the post-intervention assessment. The Positive and Negative Affect Scale (PANAS) is a 20-item scale that assesses positive and negative affect [35]. The PANAS has demonstrated adequate reliability and validity [36]. For this study, participants will be requested to provide "state" information by responding to items "at the present moment." ***Cognitive function*** will be assessed via the NIH Toolbox (www.nihtoolbox.org) [49]. This battery comprises measures of executive function, attention, episodic memory, language, processing speed, and working memory. Following NIH scoring guidelines, administering this battery will yield the Cognitive Function Composite Score and the Crystallized Cognition Composite Score (e.g., Picture Vocabulary and Reading Recognition), in addition to subtest scores. We will also administered The Montreal Cognitive Assessment (MoCA) to screen for dementia. The Edinburgh Handedness Inventory will also be administered to determine handedness. As part of this visit, we will measure the flicker fusion threshold, which is defined as the frequency at which an intermittent light stimulus appears to be completely steady to the observer. Participants will also be issued a brief pain questionnaire as it relates to the ongoing COVID-19 pandemic to assess how it has affected their pain and access to care for it.

Real-time assessment of sleep. During the baseline sessions, participants will be trained by study staff in the use of the OURA ring. Traditional self-report measures of sleep cannot capture real-time data under naturalistic conditions or measure fluctuations on a daily or hourly basis. Data collection on the ring offers several advantages including the capability of long-term continuous data collection, ecological validity, and cost-effectiveness. Sleep quality will be captured each day throughout the entire study. Data will be downloaded remotely or when the individual reports to the clinic during the intervention phase. Participants will start wearing the device during the baseline weeks and at each visit, their proficiency and use will be ascertained.

At the end of the session, subjects will be provided a copy of the following questionnaires for them to fill out at their convenience and bring back to their next visit:

- Sleep Diary: provides an assessment of habitual bedtimes and waketimes in a single administration questionnaire format.
- Medication Diary log sheet: records the precise date and time of the administration of the GABA/PLACEBO each day.
- Oswestry Low Back Pain Disability Questionnaire
- Report of the Task Force on Research Standards for Chronic Low-Back Pain
- Berlin Questionnaire
- Epworth Sleepiness Scale
- FOSQ-10
- PROMIS-Sleep Related Impairment

Figure 6. Sensory Assessment Session Protocol



Quantitative Sensory Testing (QST). Participants will undergo QST to determine responses to mechanical and

thermal stimuli and conditioned pain modulation (CPM) (Figure 6). QST will be performed on standardized sites using anatomical landmarks. All tests will be demonstrated and explained before being performed. All participants will be tested on the hands and feet with additional standardized testing sites chosen to include painful areas. We will randomize the order of thermal and mechanical testing. Cold pressor assessment, including conditioned pain modulation, will always occur last to avoid carryover effects. Patients' medications and current clinical pain will also be confirmed. All pain procedures are summarized in Figure 6 and will be successfully implemented as in our previous studies,[42][43][44] using a Medoc Pathway Thermal Sensory Analyzer (Ramat Yishai, Israel), and Algomed Algometer.

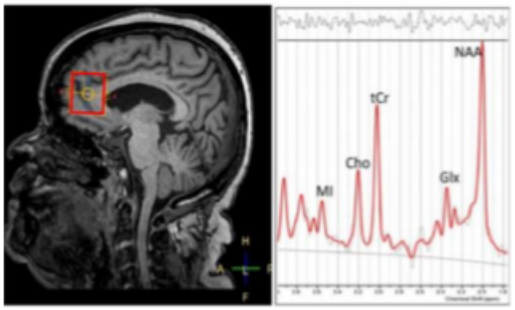
Mechanical testing procedures. Pressure pain threshold (**PPT**) will be assessed at the ipsilateral quadriceps and trapezius muscles. For all PPT measurements, after an initial practice trial, three trials will be conducted, and their average will be computed for data analysis. Using a digital, handheld, clinical grade pressure algometer (Algomed, Medoc, Ramat Yishai, Israel), the examiner will apply a constant rate (30 kPa/second) of pressure and the participant will press a button when the sensation first becomes painful, at which time the device records the pressure. Punctate Mechanical Pain will be assessed at the left thenar eminence and the left foot 2nd metatarsal head using a nylon monofilament (Touchtest Sensory Evaluator 6.65) calibrated to bend at 300g of pressure. As in our previous studies, participants will provide a pain rating following a single contact, after which they will provide another pain rating following a series of ten contacts at a rate of one contact per second. The difference between the pain rating for the single versus multiple contacts reflects temporal summation of mechanical pain. **Thermal testing procedures.** Thermal stimuli will be delivered to the left thenar eminence and the left foot 2nd metatarsal head, in randomized order, using a Medoc Pathway Thermal Sensory Analyzer (Ramat Yishai, Israel). Heat pain threshold will be assessed at each site, followed by heat pain tolerance and temporal summation. Heat pain thresholds and tolerances will be assessed using an ascending method of limits as in previous studies. Temporal summation of thermal pain will be assessed using the same stimulus parameters as previously reported by us and others.

Conditioned Pain Modulation (CPM) will be used to assess pain-inhibitory function. The conditioning stimulus will be the cold pressor task applied to the left hand, which will be tailored for each participant to achieve a stimulus that produces moderate pain (i.e., a rating of 40-60 on the 0-100 scale) and can be tolerated for a 60-second period. The test stimulus will be heat pain applied to the opposite ventral forearm, at a stimulus intensity which produces moderate but tolerable pain. First, baseline heat pain responses will be assessed, after which the participant will immerse their hand in the cold-water bath for 60 seconds. Immediately afterwards the heat pain will again be applied to the opposite arm and pain ratings will be obtained.

Short Physical Performance Battery (SPPB). We will use this brief assessment consisting of four lower-extremity function measures: standing, balance, walking speed, and ability to rise from a chair. These measures have been standardized and are widely used in older populations and have been used in our labs.

<u>Baseline Neuroimaging Assessment</u>: At the beginning of this visit, subjects will complete the following questionnaires: The state version of PANAS, the state version of the STAI, the Graded Chronic Pain Scale (GCPS), a modified version of a disability instrument called the Pepper Assessment Tool for Disability (PAT-D) as well as listing of all the current medications taken and food eaten within the past 2-4 hours and we will ask to get some information about participant's general health and sleep quality since the last visit. During this session, we will also collect a small blood sample to quantify circulating GABA concentrations. We will also take your vital signs again,and you will receive the GABA or PLACEBO capsule you are going to be taking during the next 4 weeks since this visit.

Figura 7. Frontal voxel placement for MRS acquisition and representative spectra.



We will use a state-of-the-art 3T Siemens Prisma MR system group at the McKnight Brain Institute (MBI). Anatomical image acquisition will involve a T1-weighted structural scan using a magnetization-prepared rapid gradient echo (MPRAGE) sequence, which provides good contrast between gray and white matter, and cerebrospinal fluid based on tissue T1 differences. Proton MRS: In line with procedures established in our studies (Figure 7), we will acquire single-voxel water suppressed 1H spectra (TE/TR = 35/3000ms, bandwidth =2500 Hz, 128 averages, NEX=8) using a Siemens sequence, with water T2 measurement. 1.5 cc voxels will be prescribed in two regions (frontal, insular), with voxels laterality alternated across successive patients. GABA will be extracted from frontal and insular regions of interest (ROIs) based on our previous work. Neuroimaging analysis: GABA will be quantified using the Gannet program (version 2.0) [33]. All time-domain data will be frequency- and phase-corrected using spectral registration [34], filtered with a 3-Hz exponential line broadening and zero-filled by a factor of 16. The 3-ppm GABA peak in the difference spectrum was fit using a five-parameter Gaussian model and will be quantified relative to water in institutional units. We will correct for cerebrospinal fluid (CSF) content in the voxel. Additionally, we will apply pain using quantitative sensory testing procedure during the MRI. MRI data will be used to measure the structural and functional integrity of the brain. Specific items of interest include, but are not limited to, descending sensory and motor tract integrity (fiber tractography), intracranial volume, whole brain volume, lacunae as well as metabolite concentrations.

Intervention Period: During the 4-week intervention, participants will self-administer via oral GABA 500 mg (capsule 250mg) or a placebo daily at home, at 08:00 pm. The utilized synthetic GABA is a formulation developed by "Thorne". We chose this brand as it has high-quality standards that include NSF, TGA, and cGMP certifications. The capsules are compounded free from major allergens like gluten, eggs, tree nuts, and peanuts. They also do not contain soy, dairy, yeast, shellfish, or fish. The inactive placebo will be compounded by the UF IDS Pharmacy to ensure the same capsule size and color is used for both the GABA and the placebo. Compliance will be monitored by measuring the number of capsules left in the bottle after the treatment period and through a record that participants complete each day during the intervention after the treatment period and via a log participant fill in each day during the intervention. If at any time during the treatment it is determined that the participant should not continue due to adverse events, the participant will be discontinued. Furthermore, at baseline and the end of each intervention, blood samples including renal and hepatic function will be checked to ensure that no adverse changes have occurred during the study intervention. Over the 4-week intervention period, participants will be contacted once a week to assess side effects. Any symptom reported as moderate or severe will be brought to the PI's attention and will be discussed with the study

MD as needed on a case by case basis. These weekly calls will also ensure regimen compliance and will assist participants in the download of the OURA ring data to a secure research server.

Post-Intervention Assessments: In the last week of the intervention phase, participants will be scheduled to return for their two post-intervention visits, which will be identical to the baseline visits. Importantly, at the follow-up Health and Sensory Assessment, we will assess changes in health status and their global impression of change since starting the intervention.

At study closure, participants will also be asked to guess what study medication they were taking to assess the effectiveness of blinding, followed by a full debriefing regarding the study aims. All study participants will be financially compensated for study participation. Finally, one week and three months after the last treatment phase, participants will receive a follow-up phone call to determine if any side effects occurred as well as answer a pain history, the short form of the Brief Pain Inventory, the WOMAC, PANAS and the PSQI to inquire about pain and sleep respectively. During these calls, if symptoms that indicate imminent danger to the participant are reported such as dizziness, anxiety, drowsiness, balance problems, blurred vision, itchiness, irritation or stomach pain, staff will immediately advise participants to contact emergency medical services. Simultaneously, this matter will be immediately escalated to the study physician and PI and the physician or his proxy will be in immediate contact with the participant to determine appropriate steps for follow-up.

Subjects will participate in 4 separate sessions although to reduce participant burden additional sessions may be scheduled.

Sample essays: Blood samples will be collected from the subject's antecubital vein using a butterfly catheter and EDTA-coated lavender tubes (no more than 3 tbsp collected). The samples will be separated and aliquoted in Dr. Cruz-Almeida's PAIN lab (Dental Tower). Assays will be performed in the Quest Diagnostics lab to evaluate standard clinical parameters (Comprehensive Metabolic Panel (CMP-14) while high sensitivity plasma GABA concentrations will be done using HPLC by Interdisciplinary Center for Biotechnology Research (ICBR) at UF.

Power and sample size considerations: For phase one, the estimated sample size was derived from the literature in sleep and pain studies assuming a medium effect size to achieve 80% power. For phase two of the study, we plan to recruit 28 participants, i.e., 14 participants in each of the randomly assigned treatment groups for the neuroimaging visits, this will provide effect sizes to determine the estimates of variability needed to calculate the sample size needed for future larger proposals working together with Dr. Huo.

Data Analysis: Dr. Huo will work with the study team to perform data analytic procedures for both phases. For phase one, we will employ general linear model approaches to determine associations between pain and sleep measures while controlling for relevant covariates. For phase two we will employ a repeated pre-post analysis of variance to provide the basis for future estimations of effects including multiple comparisons corrections.

Recruitment Strategy: Recruitment of participants will be accomplished using newspapers and flyers, as well as community methods similar to our previous studies and social media advertisements on Facebook that direct the user to call a lab-controlled phone number. We will also contact individuals in the PRICE registry.

6. Possible Discomforts and Risks:

Equipment used in this research meets all current safety standards, and all research staff will be highly trained in the use of all equipment. This study may include risks that are unknown at this time. Potential risks for this study are related to using of study product, neuroimaging, blood draw procedure, blood pressure measurement, the physical performance tests, the cognitive function tests, the sensory testing, and potential loss of confidentiality related to study participation, as discussed in detail below.
All assessments will be conducted in Dr. Cruz-Almeida's PAIN laboratory (Dental Tower) and the McKnight Brain Institute and all sessions will be conducted by trained and certified research staff, which will monitor potential adverse experiences and symptoms. During the testing sessions, a fully equipped defibrillator is available along with a semi-automated ECG cart. All personnel associated with the study have received CPR training and training on management of acute events including syncope, chest pain, acute dyspnea, focal neurological symptoms, and abnormal vital signs. Portable defibrillators are available at the assessment site. Additionally, a study physician is available on call and contact numbers for emergency services are posted. Institutional and community EMS services will be activated if needed. If participants develop chest pain, shortness of breath, or dizziness at any point during a screening or assessment visit, they will be instructed to rest and to contact the center and their physicians if these symptoms persist or recur.

Participants will be instructed to talk with the investigators about any discomforts that occur during the study. If for any reason the participant reports an injury, dizziness, anxiety, drowsiness, dry mouth, balance problems, constipation, blurred vision, itchiness, irritation or stomach pain, staff will immediately advise participants to contact emergency medical, they will be referred to their doctor, or the PI will call the doctor or other health care provider.

Before beginning data collection, all study coordinators undergo standardized training on all study procedures. A detailed checklist for each data collection element is in place to ensure all study coordinators are appropriately trained and able to conduct study procedures. Research coordinators will be certified in each element of the study visit including obtaining informed consent, administering questionnaires, protecting the confidentiality of collected data, performing the test batteries. Any study coordinator who is found to not adhere to all aspects of the protocol will be required to complete additional training followed by re-certification.

All research staff complete human subjects training required by The University of Florida institutional review board (IRB) and the National Institutes of Health (NIH). This training includes education about the importance of maintaining the confidentiality of personal health information. The study principal investigators or a co-investigator will be available to answer questions that arise during the informed consent process as needed. More information about specific protective measures against risk is outlined below.

GABA oral supplement administration

Gamma-aminobutyric acid (GABA) has become widely available as a food supplement. In the United States, GABA is considered a "food constituent" and a "dietary supplement," respectively. These GABA food supplements can be purchased online via numerous websites, including webshop giants such as Amazon.com, with often very positive customer reviews. Hundreds of people report that these supplements have helped them alleviate anxiety and/or improve sleep quality, in addition to other beneficial effects.

Physiological Effects of GABA. In recent years researchers have reported several placebo-controlled studies in which GABA was administered as a food supplement to healthy participants and participants with a history of acrophobia. One study found an increase in alpha waves in healthy participants and

increased levels of immunoglobulin A (IgA; an indicator of immune system functioning) in participants with a history of acrophobia when they were exposed to heights [50]. Another study reported reduced heart rate variability and salivary chromogranin A (CgA) during an arithmetic task compared to a control group after the administration of GABA-enriched chocolate [51]. Additionally, participants who received 50 mg of GABA dissolved in a beverage reported less psychological fatigue after completion of the task [52].

Safety of GABA oral supplement. No significant adverse events were reported in the above studies, indicating that GABA oral supplements are generally safe. Currently, there is no established dose for GABA as a dietary supplement, and doses in the literature range from 500 to 750 milligrams taken up to two times a day. As a precaution in our preliminary study, we decided to administer the lower dose of 500 mg daily.

Excluded Medical Conditions. As a precaution, we will exclude participants who take hypertension medications since GABA can reduce blood pressure levels. We will exclude participants that ingest neuropathic pain medication as well as anticonvulsants and antidepressants.

Drug-Interactions. It does not have any known drug interactions. However, we should know about any other medications or supplements participants are taking, including prescription drugs, nonprescription drugs, vitamins, and dietary or herbal supplements. Even though there are currently no known interactions, it is important to understand that gamma-aminobutyric acid supplementation has been studied very little in humans.

Placebo oral administration

This study compares an active drug (GABA) to a placebo. A placebo is an inactive substance made to look/taste like an active medicine.

Laboratory tests. Participants will have blood drawn at screening and during the post-intervention visit for both intervention periods to measure their blood chemistry. Abnormal results will be brought to the principal investigator's attention immediately. The results will be reviewed and signed by the study clinician and Dr. Cruz-Almeida.

Assessment of Adverse Events. A standard operating procedure will be established which is followed to collect and deal with adverse events during the research project. In particular, adverse events will be systematically monitored both during the treatment phases, as well as 3 months following study completion. In particular, participants will respond to a side effect checklist to detect any possible physiological reactions related to the drug administration. This will include a series of open-ended questions asked by trained research staff regarding any adverse events that have occurred since the last visit or phone contact. Additionally, during the 3 months follow up, participants will be asked to the WOMAC PANAS and PSQI questionnaires to assess pain, feelings, and sleep respectively. This report will be reviewed by the principal investigator and study physician in a timely fashion. Any serious untoward event, whether related or unrelated to the study drug or procedures, will be reported to the UF IRB.

Adverse events will be defined as any physical symptoms or side effects that began following the administration of the study drug. All reported and observed adverse events will be tracked in a running adverse events participant log, which will contain information regarding dates, description, and severity. All adverse events will be coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of participants reporting treatment-

emergent adverse events will be tabulated by treatment, system organ class, and MedDRA-preferred term. Treatment-emergent adverse events will be those adverse events that begin or worsened following the first dose of study drug. Adverse events will be further classified by severity and investigator-assigned relationship to study drug. All reported and observed adverse events will be tracked on a running adverse events log (specific to each subject and maintained in his/her study file) and will contain information regarding onset/offset dates, time course (i.e., single, sporadic), severity, action taken regarding study drug, relationship to study drug, and whether it meets FDA criteria for "Serious." Each reported event is reviewed by the principal investigator and the study physician in a timely fashion. Additionally, the principal investigator reviews all adverse events recorded in each participant's log after study participation.

In Case of Emergency. Participants will have 24-hour access to emergency care and will be provided with a means of contacting the on-call study doctor and research staff. Participants will be informed and encouraged to contact the study physician and study staff immediately with medical concerns or unusual reactions. Participants will also be informed of the closest Emergency Department location to their residence.

Data and Safety Monitoring Plan. A Data Safety Monitoring Plan will be in place. In particular, the following procedures will be implemented to ensure data and participant safety. Study progress and safety will be reviewed by the principal investigators in collaboration with a physician, and the study MD. We will stop the intervention if 30% or more of the participants in the GABA condition report seven or more (out of forty-four) of the side effects at moderate to severe levels over more than 3 days as acquired during the weekly check-in phone calls during the intervention phase. Data collected before the stop of intervention will be used for analysis. All participants who went through the intervention phase of the study will be followed up by phone calls for 7 days to ensure safety. Progress reports, including participant recruitment, retention/attrition, and adverse events will be provided to an Independent Safety Monitor for reviews on a bi-annual basis. The Independent Safety Monitor for this study will consist of an established senior investigator not associated with our study. A study end report will be compiled and will include a list and summary of adverse events. Also, this report will address: (1) whether adverse event rates are consistent with pre-study assumptions; (2) reason for dropouts from the study; (3)whether all participants met entry criteria; (4) whether continuation of the study is justified on the basis that additional data are needed to accomplish the stated aims of the study; and (5) conditions whereby the study might be terminated prematurely. The annual report will be signed by the Independent Safety Monitor and will be forwarded to the IRB, NIH, and FDA. The Data Safety Monitoring Plan will also require that all significant serious adverse events that may be possibly related to the study participants will be reported to the IRB, FDA, and NIH within 48 hours of the principal investigator's learning of the event. Besides, any unanticipated serious adverse events that may increase the risk of the research for participants or potential participants will be reported to the IRB and the NIH within 48 hours of the principal investigators being informed about the event. This study will be stopped before its completion if: (1) the intervention is associated with adverse effects that significantly impact the risk-benefit ratio, (2) study recruitment or retention becomes futile, (3) any new information becomes available during the trial that necessitates stopping the trial; or (4) if independent safety monitor indicates stopping trial is necessary due to adverse event frequency or severity.

ClinicalTrials.gov Requirements. Under Public Law 110-85 and NIH guidelines, the proposed research will be registered with ClinicalTrials.gov before the commencement of study procedures involving participants

Magnetic Resonance Imaging (MRI)/ Magnetic Resonance Spectroscopy (MRS)

MRI and MRS are used routinely for medical care and are very safe for most people, but participants will be monitored during the entire scan in case any problems occur. The risks of MRI/MRS are:

- The scanner contains a very strong magnet. Participants may not be able to have the MRI/MRS if they have any type of metal implanted in their body, for example, any pacing device (such as a heart pacer), any metal in their eyes, or certain types of heart valves or brain aneurysm clips. Therefore, participants will be extensively screened. Participants who would normally be excluded from getting an MRI/MRS for safety reasons will be excluded, applying criteria for an exclusion that are more stringent than those imposed for standard clinical MRI/MRS scans.
- There is not much room inside the scanner. Participants may be uncomfortable if they do not like to be in close spaces ("claustrophobia"). Participants will be screened for known claustrophobia.

The scanner produces a loud hammering noise, which has produced hearing loss in a very small number of people. Participants will be given earplugs to reduce this risk. Also, they will be informed of this possibility in the inform consent form and that they may immediately withdraw from the study at any time. During the procedure, participants will be able to talk with the staff through a speaker system, and, in the event of an emergency, participants can tell them to stop the scan.

During neuroimaging, participants will be situated comfortably on the scanner table, with a head-mounted. Brain image acquisition will take place on a 3T Siemens Prisma human imaging system at AMRIS, at the McKnight Brain Institute, employing pulse sequences and hardware that have been approved by the FDA for human clinical use. All MRI/MRS safety guidelines and precautionary steps established by the AMRIS will be strictly followed. At the end of the session, a post-scan debriefing questionnaire will be administered that examines discomfort during and after the scanning.

Blood Draw

The risks of drawing blood from a vein include discomfort at the site of puncture; possible bruising and swelling around the puncture site; rarely an infection; and, uncommonly, faintness from the procedure.

Blood Pressure Measurement

The risks of placing a blood pressure cuff on a participant’s arms are that it may cause pinching or slight bruising.

Physical Tests

There is a risk of losing balance and falling or development of chest discomfort due to coronary ischemia or dyspnea due to heart failure or lung disease associated with the physical performance-based testing (e.g., the ¼ mile walk test, balance tests, rising from a chair). We will minimize this risk by: (1) safely escorting participants to chairs located along the walking course should they become unsteady; (2) following participants at a close distance; and, (3) being at participants’ side should they need assistance. Research staff members will be trained in the conduct of the physical performance tests before they work with study participants. Study staff members are trained not to perform these tests if they feel that testing is unsafe. Besides, participants will be asked whether they feel the test is safe. Those who state it may be unsafe will not be allowed to complete the test. Staff members will be trained to protect against falling and will be trained in CPR. They will be trained in activating the emergency response system at the research facility.

Sensory Testing

The sensory testing procedures may be uncomfortable or unpleasant, in that participants may experience some temporary discomfort from the thermal, pressure, and mechanical stimulation. However, if the participants feel the sensation is greater than they wish to tolerate, they can stop any of the procedures at any time.

Personal Information

Some of the question's participants will be asked may be personal and may make participants feel uncomfortable. Time will be made to talk with the participant if they appear to be distressed. We will be asking for information about sensitive issues, such as mood which may make participants feel uncomfortable. If they are uncomfortable answering these questions, they can choose not to answer and discontinue participation in the study. Some people, when asked such questions, experience strong emotional reactions that may require counseling. If they do, they are strongly encouraged to tell the Principal Investigator, who can make an appropriate referral to the Psychology Clinic or the UF Counseling & Wellness Center at (352) 392-1575. If we should discover, based on the questionnaires or formal clinical interview, that the participant experiences marked depression or suffer from another psychiatric condition, we will offer to make an appropriate medical, psychiatric, and/or psychological referral.

Confidentiality

Data that will be collected from human subjects for this project will include behavioral performance measures, rating scales assessed through interviews and patients' responses to self-rated scales, physiological, and neuroimaging data. Data will be collected specifically for the proposed research project. Access to individually identifiable private information about human subjects will be limited to research staff affiliated with the project. Research records will be kept confidential to the extent provided by law. The collection and submission of medical information will be accomplished with strict adherence to professional standards of confidentiality. Participants' medical information will be kept in a secure location accessible only to research staff associated with this study. Participants will only be identifiable by ID number, and any published findings resulting from the study will not refer to or identify individuals. Several methods will be employed to maintain the confidentiality of participants. First, data will be collected in secure spaces where the session cannot be overheard. Secondly, only study investigators and key research staff (i.e. data manager and study programmers) will have access to the study database. Third, participants will be assigned a unique study identifier. Individual names are not linked with collected data in the password-protected study database and only the unique study identifier will be used. A file linking the participant name and contact information and their specific study identifier will be kept separately and will be password protected and only accessible to study team members. Fourth, collected data will be maintained in locked computer files and file cabinets to which only study team members have access. Collected data will be used only for research purposes. Published data will not contain any individual identifiers. Finally, all research staff members have to retake refresher course certification exams every year.

Informed Consent

Before entry in the trial, the investigator(s) or study coordinator(s) will explain to potential participants the aims, methods, reasonably anticipated benefits, and potential hazards of the trial and any discomfort it may entail. Subjects will be informed that their participation in the study is entirely voluntary and that they may withdraw consent to participate at any time. They will be told that competent physicians/lab personnel will examine their records but that personal information will be treated as strictly confidential and will not be publicly available. Subjects will be allowed to ask questions and will be given sufficient

time to review all of the relevant information associated with the study. After this explanation and before entry to the trial, the subject's consent will be obtained and documented via the signature of an informed consent form by both the subject and the person conducting the informed consent discussion. If signed informed consent cannot be obtained, the subject will not be included in the trial.

7. Possible Benefits:

There are no direct benefits for study participation. There may be benefits that we are not yet aware of. The report about the results of the study will be made available to study participants as well as others in the community. However, the greatest benefit will be to the society as a whole. Scientific knowledge advances slowly, but study results will increase our understanding of the underlying neurobiological mechanisms in sleep disorder and chronic pain in aging. Such knowledge may be implemented in intervention programs that may have the potential to increase function and personal well-being.

8. Conflict of Interest:

There are no conflicts of interest in this project.

References

[1] J. L. Riley, C. D. King, F. Wong, R. B. Fillingim, and A. P. Mauderli, "Lack of endogenous modulation and reduced decay of prolonged heat pain in older adults," Pain, vol. 150, no. 1, pp. 153–160, Jul. 2010.
[2] A. B. Neikrug and S. Ancoli-Israel, "Sleep disorders in the older adult - A mini-review," Gerontology, vol. 56, no. 2, pp. 181–189, 2010.
[3] S. K. Roepke and S. Ancoli-Israel, "Sleep Disorders in the elderly," Indian J Med Res 131, 2010.
[4] S. J. Enna and K. E. McCarson, "The Role of GABA in the Mediation and Perception of Pain," Advances in Pharmacology, vol. 54. pp. 1– 27, 2006.
[5] M. Jessica VanArsdale, MD, "Self-Care Wellness Toolkit Depression and Anxiety," 2015.
[6] S. R. Dash, "The Microbiome and Brain Health : What ' s the Connection ?," Medscape Psychiatry Ment. Heal., pp. 1–6, 2015.
[7] R. E. Harris and D. J. Clauw, "Imaging central neurochemical alterations in chronic pain with proton magnetic resonance spectroscopy.," Neurosci. Lett., vol. 520, no. 2, pp. 192–6, Jun. 2012.
[8] M. Thiaucourt et al., "Posterior Insular GABA Levels Inversely Correlate with the Intensity of Experimental Mechanical Pain in Healthy Subjects.," Neuroscience, vol. 387, pp. 116–122, 2018
[9] Evert Boonst, Roy de Kleijn,Lorenza S. Colzato, Anneke Alkemade, Birte U. Forstmann,Sander Nieuwenhuis, " Neurotransmitters as food supplements: the effects of GABA on brain and behavior", Frontiers in Psychology, Vol 6, Oct. 2015.
[10] H. M. Alshuft, L. A. Condon, R. A. Dineen, and D. P. Auer, "Cerebral cortical thickness in chronic pain due to knee osteoarthritis: The effect of pain duration and pain sensitization," PLoS One, vol. 11, no. 9, pp. 1–16, 2016.
[11] D. T. Plante, J. E. Jensen, and J. W. Winkelman, "The Role of GABA in Primary Insomnia," Sleep, vol. 35, no. 6, pp. 741–742, 2012.
[12] J. W. Winkelman et al., "Reduced brain GABA in primary insomnia: Preliminary data from 4T proton magnetic resonance spectroscopy (1HMRS)," Sleep, vol. 31, no. 11, pp. 1499–1506, Nov. 2008.
[13] C. B. Saper, T. E. Scammell, and J. Lu, "Hypothalamic regulation of sleep and circadian rhythms," Nature, vol. 437, no. 7063. Nature Publishing Group, pp. 1257–1263, 27-Oct-2005.

[14] N. K. Sharma, K. McCarson, L. Van Dillen, A. Lentz, T. Khan, and C. M. Cirstea, “Primary somatosensory cortex in chronic low back pain - A1H-MRS study,” J. Pain Res., vol. 4, pp. 143–150, 2011.
[15] N. Tzourio-Mazoyer et al., “Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain,” Neuroimage, vol. 15, no. 1, pp. 273–289, 2002.
[16] A. Zalesky, A. Fornito, and E. T. Bullmore, “Network-based statistic: Identifying differences in brain networks,” Neuroimage, vol. 53, no. 4, pp. 1197–1207, Dec. 2010. [17] A. Di Martino et al., “Functional connectivity of human striatum: A resting state fMRI study,” Cereb. Cortex, vol. 18, no. 12, pp. 2735–2747, 2008.
[18] D. Borsook, J. Upadhyay, E. H. Chudler, and L. Becerra, “A key role of the basal ganglia in pain and analgesia--insights gained through human functional imaging.,” Mol. Pain, vol. 6, p. 27, May 2010.
[19] L. Wang, K. Wang, J.-H. Liu, and Y.-P. Wang, “Altered Default Mode and Sensorimotor Network Connectivity With Striatal Subregions in Primary Insomnia: A Resting-State Multi-Band fMRI Study,” Front. Neurosci., vol. 12, no. December, pp. 1–8, 2018.
[20] C. Li, M. Dong, Y. Yin, K. Hua, S. Fu, and G. Jiang, “Abnormal whole-brain functional connectivity in patients with primary insomnia,” Neuropsychiatr. Dis. Treat., vol. 13, pp. 427–435, 2017.
[21] C. J. Starr et al., “The contribution of the putamen to sensory aspects of pain: Insights from structural connectivity and brain lesions,” Brain, vol. 134, no. 7, pp. 1987–2004, 2011.
[22] L. Amorim et al., “Poor Sleep Quality Associates With Decreased Functional and Structural Brain Connectivity in Normative Aging: A MRI Multimodal Approach,” Front. Aging Neurosci., vol. 10, p. 375, 2018.
[23] D. C. Turk et al., “Core outcome domains for chronic pain clinical trials: IMMPACT recommendations,” Pain, vol. 106, no. 3, pp. 337–345, 2003.
[24] R. H. Dworkin et al., “Core outcome measures for chronic pain clinical trials: IMMPACT recommendations,” Pain, vol. 113, no. 1–2. pp. 9– 19, Jan-2005.
[25] R. H. Dworkin et al., “Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations.,” J. Pain, vol. 9, no. 2, pp. 105–21, Feb. 2008.
[26] J. S. Gewandter et al., “Research design considerations for chronic pain prevention clinical trials: IMMPACT recommendations.,” Pain, vol. 156, no. 7, pp. 1184–97, Jul. 2015. [27] T. Hadjistavropoulos et al., “An interdisciplinary expert consensus statement on assessment of pain in older persons.,” Clin. J. Pain, vol. 23, no. 1 Suppl, pp. S1-43, Jan. 2007.
[28] R. B. Fillingim et al., “The ACTTION-American Pain Society Pain Taxonomy (AAPT): an evidence-based and multidimensional approach to classifying chronic pain conditions.,” J. Pain, vol. 15, no. 3, pp. 241–9, Mar. 2014.
[29] R. H. Dworkin, S. Bruehl, R. B. Fillingim, J. D. Loeser, G. W. Terman, and D. C. Turk, “Multidimensional Diagnostic Criteria for Chronic Pain: Introduction to the ACTTION–American Pain Society Pain Taxonomy (AAPT),” Journal of Pain, vol. 17, no. 9. pp. T1–T9, 2016.
[30] L. J. Ware, C. D. Epps, K. Herr, and A. Packard, “Evaluation of the Revised Faces Pain Scale, Verbal Descriptor Scale, Numeric Rating Scale, and Iowa Pain Thermometer in older minority adults.,” Pain Manag. Nurs., vol. 7, no. 3, pp. 117–25, Sep. 2006.
[31] N. Bellamy, W. W. Buchanan, C. H. Goldsmith, J. Campbell, and L. W. Stitt, “Validation study of WOMAC: A health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee,” J. Rheumatol., vol. 15, no. 12, pp. 1833–1840, 1988.

[32] S. Nair et al., “ROAMM: A software infrastructure for real-time monitoring of personal health,” in 2016 IEEE 18th International Conference on e-Health Networking, Applications, and Services, Healthcom 2016, 2016.
[33] J. L. Riley, M. E. Robinson, and M. E. Geisser, “Empirical subgroups of the Coping Strategies Questionnaire-Revised: a multisample study.,” Clin. J. Pain, vol. 15, no. 2, pp. 111–6, Jun. 1999.
[34] B. G. Beck AT, Steer RA, “Beck Depression Inventory-Second Edition (BDI-II) Men’s Health Initiative.” 1996.
[35] J. R. Crawford and J. D. Henry, “The positive and negative affect schedule (PANAS): construct validity, measurement properties and normative data in a large non-clinical sample.,” Br. J. Clin. Psychol., vol. 43, no. Pt 3, pp. 245–65, Sep. 2004.
[36] D. Watson, L. A. Clark, and A. Tellegen, “Development and Validation of Brief Measures of Positive and Negative Affect: The PANAS Scales,” J. Pers. Soc. Psychol., vol. 54, no. 6, pp. 1063–1070, 1988.
[37] G. M. Kiebzak, L. M. Pierson, M. Campbell, and J. W. Cook, “Use of the SF36 general health status survey to document the health-related quality of life in patients with coronary artery disease: Effect of disease and response to coronary artery bypass graft surgery,” Hear. Lung J. Acute Crit. Care, vol. 31, no. 3, pp. 207–213, 2002.
[38] E. Diener, R. A. Emmons, R. J. Larsem, and S. Griffin, “The Satisfaction With Life Scale,” J. Pers. Assess., vol. 49, no. 1, pp. 71–75, 1985.
[39] D. J. Buysse Charles F Reynolds Ill, T. H. Monk, S. R. Berman, and D. J. Kupfer, “The Pittsburgh Sleep Quality Index: A New Instrument for Psychiatric Practice and Research,” 1988.
[40] N. C. Netzer, R. A. Stoohs, C. M. Netzer, K. Clark, and K. P. Strohl, “Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome,” Ann. Intern. Med., vol. 131, no. 7, pp. 485–491, Oct. 1999.
[41] M. W. Johns, “A new method for measuring daytime sleepiness: The Epworth sleepiness scale,” Sleep, vol. 14, no. 6, pp. 540–545, 1991.
[42] Y. Cruz-Almeida et al., “Psychological profiles and pain characteristics of older adults with knee osteoarthritis,” Arthritis Care Res., vol. 65, no. 11, pp. 1786–1794, Nov. 2013. [43] J. S. Cardoso et al., “Experimental pain phenotyping in community-dwelling individuals with knee osteoarthritis,” Pain, vol. 157, no. 9, pp. 2104–2114, 2016.
[44] Y. Cruz-Almeida et al., “Racial and ethnic differences in older adults with knee osteoarthritis,” Arthritis Rheumatol., vol. 66, no. 7, pp. 1800– 1810, Jul. 2014.
[45] Y. Cruz-Almeida, M. L. Black L., E. A. Christou A., and D. J. Clark J., “Site-specific differences in the association between plantar tactile perception and mobility function in older adults,” Front. Aging Neurosci., vol. 6, no. APR, p. 68, 2014.
[46] Y. Cruz-Almeida et al., “Physical performance and movement-evoked pain profiles in community-dwelling individuals at risk for knee osteoarthritis.,” Exp. Gerontol., vol. 98, pp. 186–191, 2017.
[47] Lan Yu, Buysse, Daniel J, Germain, Anne, Moul, Douglas E, Stover, Angela Dodds, Nathan E, “Development of Short Forms from the PROMIS Sleep Disturbance and Sleep-Related Impairment Item Banks”, Behav Sleep Med.; 10(1): 6–24. December 28, 2011.
[48] Chasens, Eileen R., Ratcliffe, Sarah J., Weaver, Terri E., “Development of the FOSQ-10: A short version of the functional outcomes of sleep questionnaire”, Sleep; Vol 32, pp 915-919, 2009.
[49] Weintraub S, Dikmen SS, Heaton RK, et al. “The cognition battery of the NIH toolbox for assessment of neurological and behavioral function: validation in an adult sample”. *J Int Neuropsychol Soc.*;20(6):567-578, 2014

[50] Abdou AM1, Higashiguchi S, Horie K, Kim M, Hatta H, Yokogoshi H. “Relaxation and immunity enhancement effects of gamma-aminobutyric acid (GABA) administration in humans”. Biofactors, 26(3):201-8, 2006
[51] Nakamura H., Takishima, T. Kometani, T. Yokogoshi, H. “Psychological stress-reducing effect of chocolate enriched with γ-aminobutyric acid (GABA) in humans: Assessment of stress using heart rate variability and salivary chromogranin A”. International Journal of Food Sciences and Nutrition, 106-113, 2009.
[52] Boonstra, Evert de Kleijn, Roy Colzato, Lorenza S. Alkemade, Anneke Forstmann, Birte U. Nieuwenhuis, Sander, “Neurotransmitters as food supplements: the effects of GABA on brain and behavior”, Frontiers in Psychology, 6-11, 2015.
[53] Kerns, Robert D., Turk, Dennis C., Rudy, Thomas E, “The West Haven-Yale Multidimensional Pain Inventory (WHYMPI)”, Journal of Pain, vol. 23, no. 4. pp. 345-356, 1985.