

Testing Biological and Psychological Pathways of Emotion Regulation as a Primary Mechanism of Action in Yoga Interventions for Chronic Low Back Pain: A Randomized Controlled Trial

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Table of Contents

Original Manuscript..... 5

Supplementary Files..... 34

 Figures 35

 Figure 1..... 36

 Figure 2..... 37

 Figure 3..... 38

 Figure 4..... 39

 Multimedia Appendixes 40

 Multimedia Appendix 1..... 41

 Multimedia Appendix 2..... 41

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Abstract

Background: Interventions that promote adaptive emotion regulation (ER) skills reduce pain in chronic pain patients; however, whether effects of yoga practice on chronic low back pain (CLBP) are due to improvements in ER remains to be examined.

Objective: This study will test whether yoga's effects on CLBP (improved pain severity and interference) are mediated by improved ER, the extent to which effects are related to specific aspects of ER, and the role of pain sensitization as a mediator or moderator of effects. In this study, pain sensitization will be assessed by quantitative sensory testing and gene expression profiles to examine whether pain sensitization moderates yoga's effects on pain or whether yoga and ER abilities reduce pain sensitization leading to decreased pain severity and interference.

Methods: For this two-arm parallel group blinded randomized controlled trial, we will enroll 204 adults with CLBP who will be randomized to receive the yoga (n=102) or a control stretching/strengthening (n=102) intervention, which are delivered via online synchronous biweekly 75-minute sessions over 12 weeks. Participants are encouraged to practice postures/exercises for 25 minutes on other days using accessible pre-recorded practice videos that are sent to participants electronically. Participants will be assessed at five timepoints: baseline, mid-intervention (6 weeks), post-intervention (12 weeks), and 3- and 6-month follow-ups. Assessments of emotion regulation, pain severity and interference, pain sensitivity including somatosensory and gene expression profiles, and physical strength/flexibility will be conducted at each visit. Fidelity of the interventions are assessed using a manualized checklist to evaluate recorded group sessions to ensure consistent instructor delivery.

Results: The primary outcome will be the mean change in pain severity as measured by the Brief Pain Inventory-Short Form at 12 weeks. The primary mechanism of action is ER measured by change in the Difficulties in Emotion Regulation Scale (DERS) total score. Secondary outcomes include pain sensitivity, physical strength/flexibility, pain interference, and quality of life. A mediation path analysis and series of moderated mediation path analyses will be conducted to test the study hypotheses. As of January 2024, we have enrolled 138 participants. We expect the study to be completed by May 2025.

Conclusions: The study will provide important data for evaluating whether improvements in ER are responsible for reduced pain perception and pain sensitivity as well as increased quality of life in the context of chronic pain. The study findings have important implications for determining the mechanism of action for yoga, and possibly other mind-body interventions as non-pharmacological therapies for pain management. Results of the study will inform the content, delivery, and measures for intervention trials involving yoga as a modality for relieving pain and improving function. Clinical Trial: This study is registered

on ClinicalTrials.gov with the number NCT04678297.

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Original Manuscript

Testing Biological and Psychological Pathways of Emotion Regulation as a Primary Mechanism of Action in Yoga Interventions for Chronic Low Back Pain: A Randomized Controlled Trial

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Abstract (450 words)

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mediation path analysis and series of moderated mediation path analyses will be conducted to test the study hypotheses. As of January 2024, we have enrolled 138 participants. We expect the study to be completed by May 2025.

Conclusions: The study will provide important data for evaluating whether improvements in ER are responsible for reduced pain perception and pain sensitivity as well as increased quality of life in the context of chronic pain. The study findings have important implications for determining the mechanism of action for yoga, and possibly other mind-body interventions as non-pharmacological therapies for pain management. Results of the study will inform the content, delivery, and measures for intervention trials involving yoga as a modality for relieving pain and improving function.

Trial Registration: ClinicalTrials.gov NCT04678297.

Keywords: chronic low back pain, emotion regulation, mind-body interventions, yoga

Introduction

Yoga has been shown to reduce pain and improve function in populations with chronic low back pain (CLBP) in multiple randomized controlled trials [1,2]. However, results vary and effects are generally modest [3]. This variation is perhaps due to differences in the specific neurobiological mechanisms through which yoga exerts clinical improvements on pain that are affected by different yoga interventions. These mechanisms, which have been only minimally identified, could potentially be harnessed to achieve more consistent and optimal outcomes from yoga interventions. The one study that examined mediators of yoga's effects on pain lacked strong theoretical bases for assessment of the mechanism(s) involved [4]. Using a comprehensive theoretical emotion regulation (ER) model of yoga [5], we are conducting the first test of ER as a primary mechanism of yoga's effects on CLBP. We will also test the role of pain sensitization using somatosensory and gene expression profiles in this model [6] and examine specific aspects of ER.

Emotion regulation refers to “extrinsic and intrinsic processes responsible for monitoring, evaluating, and modifying emotional reactions, especially their intensive and temporal features, to accomplish one's goals” [7]. Emotions strongly influence perceptions of pain intensity and predict disability [8], particularly among individuals with CLBP [9,10]. Interventions that promote adaptive ER skills reduce pain in chronic pain patients [11]. Increasing evidence demonstrates that consistent yoga practice can promote improved ER [12, 13] but research has not yet tested whether effects of yoga practice on CLBP are due to improvements in ER.

An integrative model of yoga's effects on emotion regulation

Given the importance of ER in managing chronic pain and yoga's demonstrated promotion of improved ER, we developed an integrative model of yoga's effects on CLBP that highlights the key role of ER. Previous work by our team [14, 15] and others [16] demonstrated that yoga simultaneously comprises multiple components and that physical activity (poses and transitions between poses), breathwork and meditation are all important therapeutic elements. Thus, although

physical activity interventions alone have demonstrated salutary effects on negative emotion [17] and ER [18,19], yoga's inclusion of breathwork and meditation along with physical activity may more potently improve ER [5].

Yoga provides myriad opportunities to develop ER skills helpful to people managing chronic pain. Practitioners can learn how to experience sensation without negative evaluative judgments, cultivating nonreactivity. Due to cognitive priming and reinforcement during movement, yoga provides simultaneous input to cognitive, motor, and sensory pathways, which may allow practitioners to consciously influence their interpretation of sensation/pain and manage its affective dimensions. Given the myriad components of yoga that can facilitate developing ER skills, we posit that ER is a key mechanism by which yoga exerts effects on individuals with CLBP. The few studies examining links between yoga, ER, and pain supports our model (Figure 1). For example, yoga practitioners were better able to tolerate experimentally induced pain than were non-practitioners, with corresponding greater left intrainular white matter connectivity [20]. Further, the yoga practitioners reported coping with the pain stimulus using (adaptive) ER strategies such as relaxation, nonjudgmental focusing, and reappraisal. Thus, the ability to minimize the affective dimensions of pain may dampen physiological responses to negative emotions such as anxiety, which have been associated with perception of pain [21,22].

Pain sensitivity may influence the effects of yoga/ER on CLBP via moderation or mediation

Recent studies document that patients with CLBP demonstrate sensory and functional alterations reflecting peripheral and central nervous system sensitization associated with enhanced pain sensitivity [23-25]. Enhanced pain sensitivity as a mechanism of CLBP includes sensitization of nociceptors and neuronal circuits [26], and increased pain signaling through membrane excitability and synaptic efficacy [27] which are conferred through altered expression of pain-sensitivity (and

immune-related) genes [6, 28]. The somatosensory changes associated with enhanced pain sensitivity in CLBP involve decreased thermal and mechanical pain thresholds at the site of pain and remote areas [25, 26].

Preliminary research suggests that negative emotion is an important determinant of pain sensitivity [29, 30], predicting up to 23% of the variance in CLBP-related disability [31, 32]. For instance, greater pain catastrophizing and anxiety are associated with lower standardized values of heat pain threshold and tolerance in patients with chronic pain [33]. In turn, negative emotions and inability to tolerate stress has been shown to activate inflammatory pathways through the release of proinflammatory cytokines and substance P [34, 35]. To date, only two small studies have examined whether yoga specifically influences pain sensitivity. However, in a systematic review of 15 RCTs, yoga was associated with decreases in interleukin (IL)-1 β , IL-6, and tumor necrosis factor- α [36]. In addition, specific components of yoga (meditation, relaxation, breathing) have been shown to alter gene expression profiles and levels of inflammatory mediators [37-39].

As seen in Figure 1, we propose that pain sensitization moderates yoga's effects on pain, in that CLBP patients with higher sensitization may benefit less [40, 41] given that their pain is more centralized [42, 43]. This is a fairly novel hypothesis with some supportive evidence [44, 45]. We will also explore the possibility that yoga and improved ER abilities might actually *improve* sensitization and thus decrease pain (Figure 2).

Little research has demonstrated that treatments for pain, including behavioral interventions, modify sensitization once it has occurred [46, 47] although a reversal of central sensitization was observed in patients with structural pain-related pathology who underwent corrective surgery [48] as well as patients with migraine and chronic pancreatitis [49, 50]. We considered alternative strategies to test these linkages. For example, a systematic review of 1037 individuals with CLBP provided moderate evidence that structural brain differences in specific cortical and subcortical areas of the brain and altered functional connectivity in pain-related areas following painful stimulation

differentiate chronic pain from pain-free individuals [51]. While brain imaging provides one way to examine changes in pain sensitivity, we assert that *identifying specific cellular mechanisms* through which emotion regulation affects pain sensitivity will generate greater translational capacity for the clinical care of individuals with CLBP.

Controlling for improvements in physical strength/flexibility

To be comprehensive, our model includes improved strength and flexibility, given that improvements in these domains are common in yoga intervention trials. In fact, yoga typically shows effects on strength, flexibility and other physical outcomes that are as substantial as those of PT or stretching-strengthening exercise groups [52, 53]. Sherman and colleagues [4] demonstrated that strength and flexibility may mediate some of yoga's effects on pain. Overall, accumulating evidence demonstrates moderate but varied effects of yoga for reducing CLBP pain and disability; much remains to be learned about *how* yoga exerts these effects and why its effects vary. Understanding the proposed MOAs of yoga will provide not only a more solid scientific basis to assure clinicians of the value of yoga to patients with CLBP and other conditions, but also important targets for intervention modification and optimization.

Objective

To address this gap, we will test the impact of a yoga intervention on ER and pain severity and functioning compared to a general stretching/strengthening intervention. This design allows us to isolate the additional effects of yoga above and beyond more general movement practices, thereby testing ER as a key mechanism of action (MOA) underlying the clinical effects of yoga on CLBP. Specifically, we will test whether yoga's effects on CLBP (improved pain severity and interference) are mediated by improved ER, the extent to which effects are related to specific aspects of ER, and the role of pain sensitization as a mediator or moderator of effects.

Stretching/strengthening exercise was selected as the active comparison intervention given that we are interested in determining not only whether yoga influences ER but also the extent to

which these effects are due to aspects of yoga above and beyond nonspecific factors (e.g., expectancies, time, attention, effort) [13] as well as improvements in strength and flexibility [4]. The two intervention groups will be similar in many aspects, but only yoga will incorporate aspects that we hypothesize will facilitate ER (e.g., breathwork, mindfulness, relaxation). We selected the hypothesized MOA based on our extensive work regarding the therapeutic characteristics of yoga and mechanisms of CLBP [5,14]. Our 3-month and 6-month follow-ups will allow us to examine whether the effects of yoga emerge later or persist. The study is highly innovative in its approach to testing the MOA of yoga for alleviating CLBP. By identifying the specific mechanisms through which yoga may influence pain, these results will facilitate optimizing interventions to improve therapeutic accuracy for prescribing and using yoga for CLBP, a highly prevalent and costly health condition in the U.S. and worldwide.

Methods

Design

This study is a two-arm parallel group blinded randomized controlled trial to examine ER as a MOA of yoga in individuals with CLBP (Figure 3). The study was approved by the Institutional Review Board of a major research-intensive university in the New England region. In total, 204 people with CLBP will be randomized to receive yoga or the stretching/strengthening intervention with assessments of pain severity and interference, ER, pain sensitivity, physical strength/flexibility, and quality of life at baseline, 6 weeks (midway through the intervention), 12 weeks (after completion of the intervention) and 3- and 6-months after the completion of the intervention. Both groups will be instructed to continue the use of any other strategies or treatments that they have been using to manage their CLBP throughout the study.

Participants

We will enroll 204 men and women aged 18 and over with nonspecific CLBP who meet eligibility (Figure 4). Nonspecific CLBP is defined as pain without a specific cause or need for

surgical intervention that is anywhere in the region of the low back bound superiorly by the thoracolumbar junction and inferiorly by the lumbo-sacral junction, which has been present for ≥ 3 months out of the prior 6 and is currently rated at a level of ≥ 2 on the numeric rating scale (NRS). Eligibility will be determined by asking the following screening questions [54]: (1) How long has back pain been an ongoing problem for you? (2) How often has low-back pain been an ongoing problem for you over the past 6 months? Responses of greater than 3 months to question 1 and “at least half the days in the past 6 months” to question 2 will define CLBP.

Recruitment and Retention Strategies

Active and passive recruitment strategies will be used to recruit individuals with CLBP including: (1) contacting CLBP participants enrolled in an IRB-approved pain registry, (2) advertisements on social media (Instagram, Facebook, Twitter, Reddit, Craigslist), (3) placing printed advertisements in public transportation vehicles and local newspapers, and (4) distributing flyers at local outpatient clinical sites and local universities. We will recruit continuously and start a new cohort every 6 months, so that there will be cohorts in both interventions and follow-up phases throughout the study. This approach will help control for seasonal effects and other potential confounds. All participants will receive a yoga/exercise mat, block, and strap prior to their first session, and \$70 following the baseline, 6- and 12- week (post-intervention) and 3- and 6-month follow-up assessments with an additional \$50 for those who complete all data collection sessions.

Interested volunteers are asked to complete an online screening questionnaire via REDCap, which includes questions to ensure they meet inclusion/exclusion criteria and can participate safely. Volunteers who are deemed eligible to participate are contacted by study staff to schedule their baseline appointment.

Ethical Considerations

Prior to completing any study procedures, all participants provide written informed consent

on a form that was approved by the Institutional Review Board at University of Connecticut (IRB#H19-191). All study procedures are in accordance with the ethical standards described by the Helsinki Declaration. Study participants are assigned an identification number, allowing all stored records to be deidentified. Deidentified data are kept in locked file room or stored in a password-protected database on a password-protected computer. All participants are monetarily compensated for their participation up to \$400 for completing all study visits. Participants can withdraw from the study at any time (Supplementary file: Informed consent form).

Procedures

Randomization and Blinding

Eligible volunteers are scheduled to meet with a study staff member who will follow all informed consent procedures. After written consent is obtained, participants are randomized to the yoga or stretching/strengthening group using a stratified randomization scheme based on biological sex to ensure balance between groups, and the assigned group is known only by the study staff managing the participant and instructor schedules.

We will employ blinding whenever possible. Assessments, evaluations, and data analysis will be conducted without the knowledge of participants' assigned group. We will blind study personnel to the assigned condition of subjects when conducting data collection by using unique study identification numbers, by following a strict script to refrain from discussing participant activities, and by using different members of the study team to coordinate assigned condition activities and to collect data. De-identified data with codes for assigned condition will facilitate blinded data analysis.

Data Collection Visits

At each study visit, venous blood samples (15 ml) will be collected in one 10-ml PAXgene vacutainer and one 6-ml K2 EDTA vacutainer by a research team member experienced in venipuncture. The samples will be immediately placed in a biohazard container and transported to the laboratory where they will be processed and stored in a -80°C freezer for bulk processing of

genetic and protein measures. Physiological and quantitative sensory measurements will be conducted by a trained research assistant (RA). Participants will be asked to complete all study questionnaires via REDCap after completion of the laboratory data collection.

Interventions

All yoga and stretching/strengthening sessions will take place on a virtual secure internet platform. This delivery modality will provide more inclusive participation and reduce barriers such as participant transportation and parking. Seventy-five minute classes for both study arms will be offered three times per week for 12 weeks. Participants will be asked to attend at least two out of three of the offered classes per week. The importance of attending two sessions per week is emphasized during the first session and throughout all subsequent sessions. Participants who repeatedly miss sessions without notifying study personnel will be contacted to check on the reason for non-attendance and to encourage resuming participation as soon as possible. Participants are encouraged to consult with the instructor individually before or after class about problems or difficulties they are encountering at home or in the formal sessions.

Participants are asked to practice exercises at home on days they do not attend formal synchronous sessions to maximize the benefit of the intervention. Participants will be emailed daily links to pre-recorded practice videos that are approximately 25 minutes in length, and asked to record the amount of time they spent on the practice videos.

Yoga intervention. The yoga intervention will be led by certified 500-hour RYT's (Registered Yoga Teachers) trained in working with back pain patients. The yoga for CLBP protocol [55] consists of classical hatha yoga with influences from vinyasa and Iyengar yoga. These yoga styles are those most commonly offered in clinical and community settings, and emphasize the importance of modifications and adaptations including the use of props such as straps and blocks to minimize the risk of injury and make the poses accessible to people with health problems and limitations [56]. The manual developed to standardize the yoga classes offered in the intervention contains pictures and a

description of how to perform each pose. The manual also includes suggested instructor dialogue, which may be paraphrased or varied slightly yet promotes consistent delivery, which enhances the replicability and generalization of results. The intervention includes some poses that could aggravate back conditions in some people if they are not modified, so multiple modifications are suggested and many poses are only worked up to after weeks of practice and individual attention from the instructor. The more challenging poses are never included in the home practice videos.

For each yoga class in the protocol, the instructor leads participants through a series of 23 yoga poses (32 total variations) at a slow-moderate pace. During the formal sessions, participants are instructed to take slow, deep breaths, timing their inhales and their exhales with specific phases of poses. Participants are encouraged to emulate optimal alignment as demonstrated by the instructor and to focus on a goal or positive direction for their yoga practice. Yoga classes are constructed to allow optimal flow from one pose to another. Each session begins with a few minutes of deep breathing and mindfulness/meditation followed by about 15 minutes of basic postures (Poses 1-8) to warm up muscles by increasing circulation to provide increasing flexibility as the class progresses. Most poses are conducted once per side. After the warm up, the instructor leads participants through a series of standing poses (Poses 9-14) for 15 minutes. After the standing poses, the class moves into floor poses (Poses 15-23) for 20 minutes. Sessions end with 5-7 minutes of complete relaxation in the standard ending pose “savasana,” during which additional positive affirmations are provided.

Stretching/strengthening control intervention. This intervention is designed to require a similar amount of physical exertion (stretching and strengthening exercises only, with no extreme movement). Classes will be led by physical therapists or other skilled therapeutic exercise instructors and involve conventional exercises appropriate for patients with CLBP, including a comprehensive set of exercises that stretch all the major muscle groups, with an emphasis on the trunk and legs. The intervention will include 12 stretching exercises used in the exercise arm of previous studies that have successfully compared exercise to yoga [57,58] (i.e., gastrocnemius, soleus, quadriceps,

posterior and inferior shoulder, upper trapezius, hip flexor, back extension, back rotation, hamstrings, hip external rotators, back flexion). It will also include 3 additional stretches (hip internal rotators, hip adductors and hip flexion). Each stretch will be held for approximately 60 seconds and repeated once. In addition to a complete set of full-body stretches, the class will begin with a five minute warm-up period consisting of basic aerobics steps (i.e., 1 minute each of walking in place, marching, lateral shuffling, turning and reaching, and box step) and will also include four exercises that strengthen the back, abdomen and hips (i.e., squats, crunches, oblique crunches, back extensions). Over the 12 weeks, the repetitions of each strength exercise are increased from 8 to 30. Specific strength exercises are practiced in separate sets of 5 to 10 repetitions.

Treatment Fidelity

All sessions will be recorded and instructor fidelity to the yoga intervention or stretching intervention manuals will be evaluated using video-recordings of sessions. Instructors and participants will be aware of and consent to the recordings. We will select one session/week from each condition for rating by trained RAs, who will review sessions using a manual checklist for instructor adherence to the manuals, using a 0-10 rating scale for each procedure or instruction. If the rating is less than 100% adherent, we will meet with the instructor to discuss the places in the session that were not adherent.

Measures

Assessments of pain intensity, pain interference, emotion regulation and other parameters will be taken at baseline, 6 and 12 weeks, and 3 and 6 months post-intervention.

Primary Outcome

Pain severity will be measured with the Brief Pain Inventory-Short Form (BPI-SF) [59] at 12 weeks. The BPI-SF has been validated with CLBP and has shown good reliability [60].

Primary Mechanism of Action

Emotion regulation as the primary mechanism of action, will be measured using the

Difficulties in Emotion Regulation Scale (DERS) score at 12 weeks. The DERS is the gold standard self-report measure of individuals' abilities to respond to emotional experiences in a goal-oriented manner [60]. The 36-item DERS taps aspects of *difficulties with emotion regulation*, which we anticipate will *lessen* with yoga practice [61]. Participants rate the extent to which each of 36 statements currently applies to them and the measure yields a total score comprising summed subscales. The DERS is sensitive to change over time in emotion regulation and internal consistency reliability is high [60].

The Negative Affective Priming Task [62] will also be used to capture individual differences in emotional attention, reactivity and appraisal, and ability to inhibit negative emotion and purposefully shift attention to more positive aspects of daily life. Participants are exposed to neutral and affective words with a strong positive and negative valence in consecutive paired trials, one word serving as the "target" and the other as a "distractor." Participants are instructed to ignore the distractor and to attend to the target in both control and negative priming conditions, with "inhibition ability" operationalized as a difference score between response latencies in control and negative priming conditions. The stronger one's inhibition abilities, the longer the latency in the negative priming condition compared to the control condition (scored in milliseconds). Individuals with chronic depression and greater tendency to engage in maladaptive rumination demonstrate reduced ability to inhibit negative, as opposed to neutral, words with no difference in the ability to inhibit positive words [63, 64].

Secondary Outcomes

There are four secondary outcomes for this study: pain sensitivity, physical strength /flexibility, pain interference, and quality of life.

Pain Sensitivity: Peripheral and central sensitivity. We will use a comprehensive Quantitative Sensory Testing (QST) battery of mechanical and thermal stimuli [65]: 1) cutaneous mechanical pain sensitivity, involving measures of tolerance, threshold, temporal summation, and after sensations; 2)

heat and cold pain sensitivity, involving threshold, tolerance, ratings of supra-threshold stimuli; and 3) pressure pain thresholds. Inter-rater reliability of the QST protocol has been reported in several clinical trials, with each individual test achieving a CI of .87-.94 [66, 67].

In addition to the QST battery, we will isolate total RNA from whole blood for sequencing at each timepoint. We will prepare libraries per Illumina standard protocols and sequence RNA on the Illumina HiSeq2500 System (Illumina Inc.) to obtain 150–base pair paired-end reads. We will examine how changes in the expression of pain sensitivity genes, as well as the entire transcriptome, differ between the experimental and control group (those with complete data from yoga vs. stretching) x sex using statistical modeling and construct a database of gene expression profiles to generate a profile of change in ER, as well as identify novel therapeutic targets for better pain management. We will use a candidate approach to examine genes identified from our preliminary studies, and a hypothesis-generating approach to identify differentially expressed genes.

Physical strength/flexibility. Physical measures include grip strength and core stabilization and strength. Grip strength will be measured using two trials for each hand with a hydraulic dynamometer. The best performance is selected for each side, and the average of the left and right hand is used for analysis. Painful or injured hands or wrists are not tested and the result of the good hand is used. Good reliability and predictive validity have been shown [68]. Core stabilization and strength will be assessed using prone and supine bridge positions [69]. Participants begin on their elbows in the prone position with shoulders, hips, and ankles aligned. The supine position is tested next, with knees flexed 90 degrees and pelvis raised from the floor with shoulders, hips, and knees aligned. Assessors record the length of time (120 seconds max) that each position is held in proper form.

Pain interference. Interference of function due to pain will be measured with the Brief Pain Inventory (BPI) [60]. The pain interference score is the mean of the 7 interference items.

Quality of Life. The 36-item Short Form Health Survey (SF-36) [70] will be administered at each

timepoint to gain a deeper understanding of the psychological, physical, and social limitations that participants experience as a result of pain. Subscales characterize participants' physical functioning, role functioning as impacted by physical and emotional health, energy/fatigue, emotional well-being, social functioning, pain, and general health. The SF-36 demonstrates excellent strong psychometric properties and predictive validity in a variety of diverse samples, including those experiencing chronic pain [71].

Exploratory Variables

Demographics, class attendance/home practice, expectancies, and substance use will be measured to examine the impact on the primary and secondary outcomes. A brief questionnaire (minimum dataset as recommended by the NIH Taskforce on Research Standards for CLBP) [54] will assess demographics (age, gender, race/ethnicity, education, and employment status) and medical/psychiatric history (comorbidities, medication usage, ongoing treatments). Attendance at yoga or stretching sessions will be assessed using attendance data from the session recordings. The Essential Properties of Yoga Questionnaire (EPYQ) [72] will be used to rate both interventions (yoga and stretching/strengthening) and measures the extent to which 14 different dimensions are emphasized in a mind-body intervention (e.g., physical challenge, breathwork, restorative postures, mindfulness). The Credibility Expectancy Questionnaire (CEQ) [73], a 6-item self-report instrument will be used to assess treatment credibility and patient expectancy for improvement [74]. In order to assess participants' use of tobacco, alcohol, prescription medicines, cannabis, and other non-prescribed substances, the Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST) [75] will be administered by study staff at each timepoint.

Statistical Analysis

Power

The primary aim is to test the null hypothesis that the two population means are equal between the yoga and stretching/strengthening groups on the primary outcome, pain severity as

measured by the BFI-SF as well as the primary MOA, ER as assessed by the DERS based on our primary measure of ER. Power calculations incorporated prior effect sizes from works by others. A proposed sample size of 102 per group, which adjusted for attrition, was calculated to detect statistically significant results with 80% power (estimated $d = .50$). In consideration of our secondary aims, we also powered the detection of paths a and b within pain interference mediation models. This was done using simulation in R ($N = 5000$). Following simulation methods ($N = 5000$) presented in Fritz and MacKinnon [76], sample size was determined by increasing simulation sample size until 90% of simulations significantly detected both paths a and b with estimated effect size magnitudes of $d = .39$ (path a) and $d = .26$ (path b) at $\alpha = .05$. A proposed sample size of 116 was calculated, which was already reached when powering our primary aim.

Data Analysis

All analyses will be performed in SPSS 29 (Chicago, Illinois). A p-value of 0.05 or less will be considered statistically significant. The primary outcome is pain severity (BFI-SF) and the primary MOA is ER (DERS). We will examine baseline demographics and study variables descriptively, and test for differences between yoga and stretching/ strengthening groups. If assumptions are met, a series of two-sided t-tests, mixed effects models, and path analyses will test our hypotheses. A mediation path analysis will be conducted examining the indirect path of group and change in ER from baseline to 6 weeks (path a), and change in ER from baseline to 6 weeks and pain severity (BPI-SF) at 12 weeks (path b) controlling for baseline pain severity. The magnitude of indirect path b will be assessed, controlling for path a and the direct path between group and change in pain severity at 12 weeks (path c') to test if changes in ER predict subsequent changes in pain severity. Identical models will be created with change in ER from baseline to 12 weeks, and pain severity at 3- and 6-month follow-ups. The magnitude of indirect path b will be compared between groups to test if the path between ER and pain severity is greater in the yoga group than the stretching/strengthening group. If 95% confidence intervals of path estimates do not contain zero,

they will be considered meaningful. Finally, a series of moderated mediation path analyses will be conducted, examining measures of baseline pain sensitivity (QST scores and normalized gene expression values), strength and flexibility, pain interference and quality of life as moderators of the identical mediation model. All analyses will also be adjusted for important covariates including, but not limited to, demographics (e.g., biological sex, race, sex), cohort, instructor, and intervention components (EPYQ) and credibility/perception of success (CEQ). Sensitivity analyses will examine whether treatment responders/non-responders differ significantly in baseline ER abilities. Baseline DERS scores will also be examined as a continuous moderator in main study analyses to establish whether some individuals may enjoy greater benefit from this intervention more than others.

Results

This project is funded by the National Center for Complementary and Integrative Health and reviewed by the University of Connecticut's institutional review board. Recruitment began in September 2020. As of January 2024, we have enrolled 138 participants. We expect the study to be completed by May 2025. No interim analyses are planned for evaluation of the primary and secondary outcomes. Analyses will be conducted following final data collection using a mediation path analysis and series of moderated mediation path analyses to examine the mechanism(s) through which yoga reduces pain.

Discussion

Yoga has been shown to decrease pain severity in individuals with CLBP. The aim of this study is to determine if ER is a mechanism of yoga by which a significant reduction in pain can be achieved. We will also determine whether yoga can lead to improvements in pain sensitivity, physical strength/flexibility, pain interference, and quality of life.

This will be the first study to assess ER as an MOA of yoga and interrogate plausible biological and psychological pathways that impact the contribution of ER on pain relief. The study

results will provide empirical data on the role of ER as a mechanism of action for yoga interventions and inform future studies on whether ER could be bolstered as a component of yoga or other mind-body interventions to improve pain outcomes.

Limitations of the study include that it will be performed at one site within the U.S. and the interventions are only delivered in English. As a first-step to determine whether ER is a MOA of yoga, the study may support evaluating or targeting ER in yoga interventions among more diverse populations, with delivery in other languages, and with other chronic pain conditions.

This two-arm parallel group blinded randomized controlled trial will examine ER as the MOA of yoga in individuals with CLBP. The study will provide important data for evaluating whether improvements in ER are responsible for reduced pain, whether pain sensitization moderates yoga's effects on pain, or if yoga and improved ER abilities reduce pain sensitivity and thereby relieves pain. The study findings have important implications for future yoga research studies, as well as other mind-body modalities designed to improve pain management.

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Data Availability

The research materials generated during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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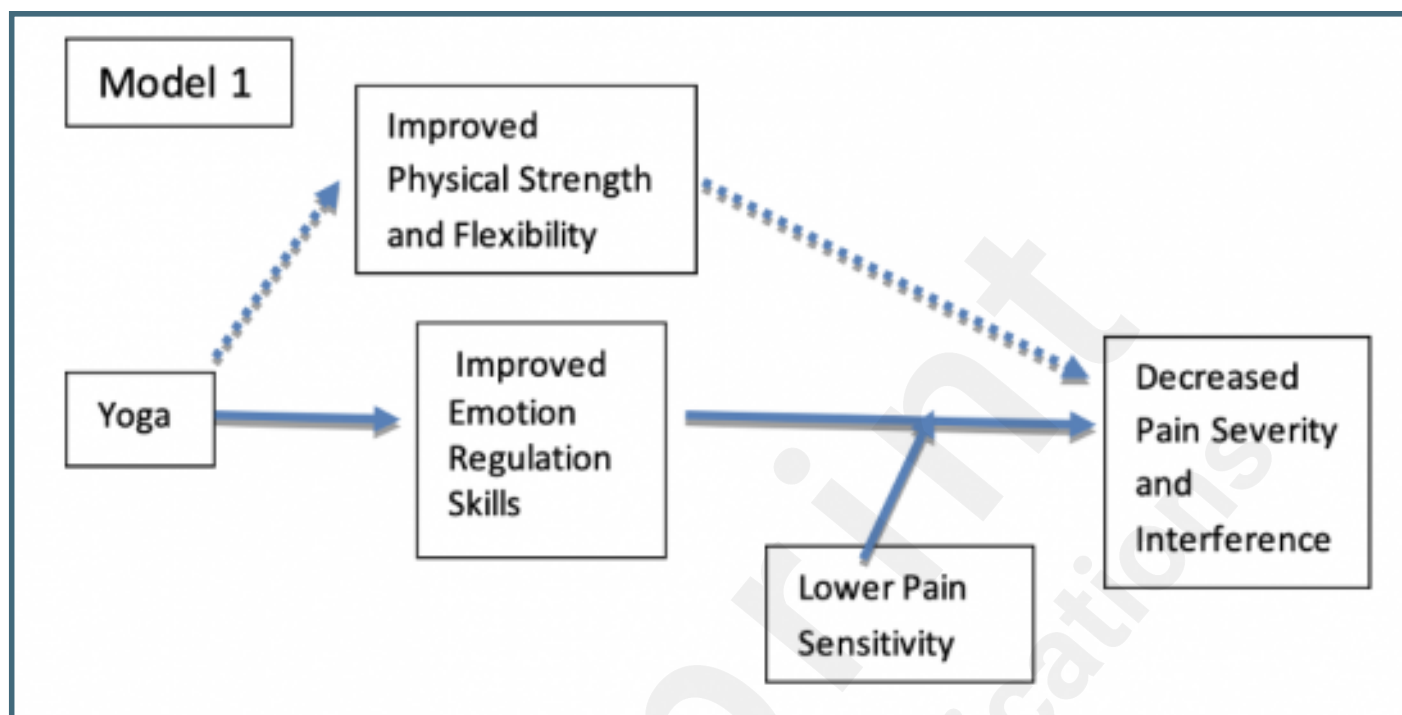
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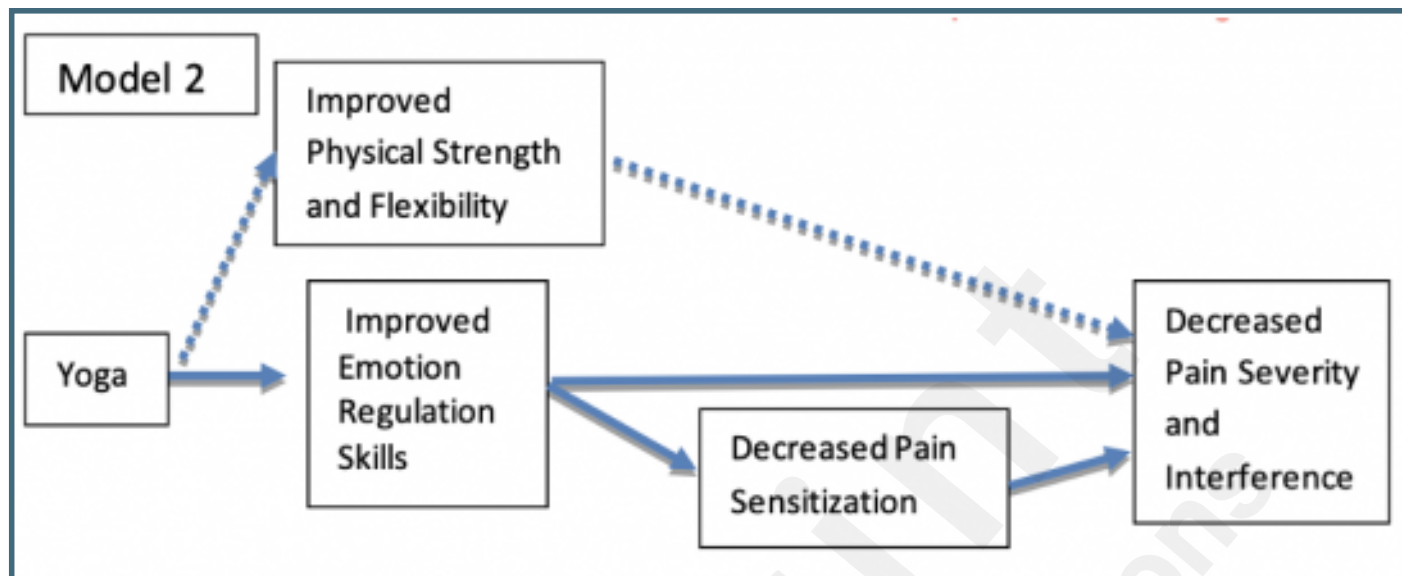
Supplementary Files

Figures

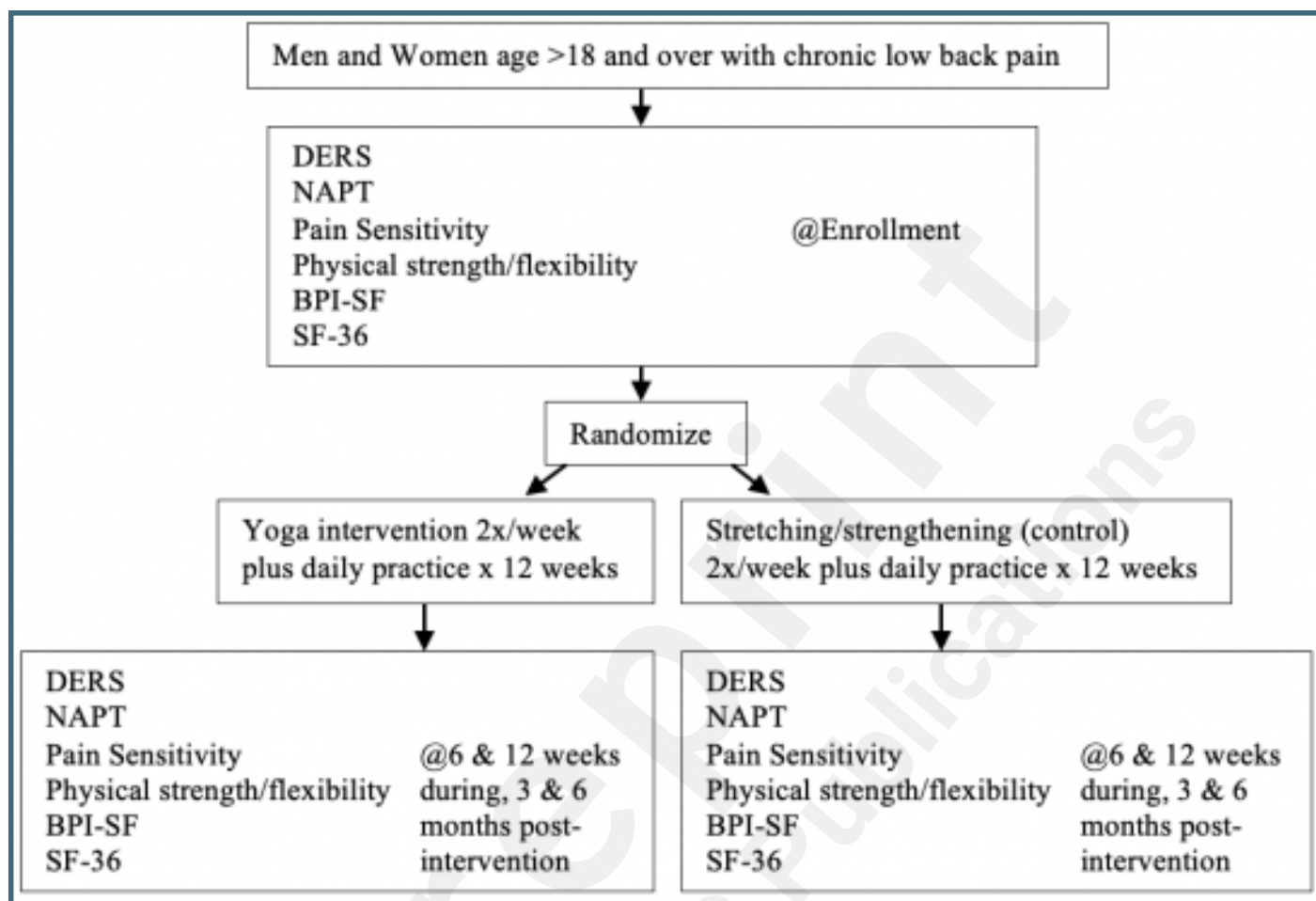
Model of primary and alternative mechanisms of action. Model 1 proposes that pain sensitization moderates yoga's effects on pain, in that chronic low back pain patients with higher sensitization may benefit less given that their pain is more centralized.



Moderated mediation model of emotion regulation. Model 2 will explore the possibility that yoga and improved emotion regulation abilities might actually improve sensitization and thus decrease pain.



Study overview. Note: DERS=Difficulties with Emotion Regulation Scale; NAPT=Negative Affective Priming Task; Pain sensitivity measured by quantitative sensory testing and blood draw for gene expression profile; BPI-SF=Brief Pain Inventory Short-form; SF-36 measures quality of life.



Inclusion / exclusion criteria to determine eligibility for study participation.

Inclusion Criteria	Exclusion Criteria
Age ≥ 18	back surgery within the last 1 year
Report of low back pain ≥ 3 of last 6 months	back pain due to specific systemic problem (e.g., lupus)
Willing to attend 12-weeks of yoga or stretching (twice per week)	lower extremity weakness (motor strength 4/5 of the quads, gluts, hamstrings, EHL)
Willing to complete 5 assessments	sciatica or (+) straight leg raise (SLR)
English Literacy	coexisting chronic pain problem (migraine headaches, fibromyalgia)
No changes in pain treatments in the past month.	Serious or unstable psychiatric illness (e.g. psychosis, mania, history of suicide attempt), current suicidal ideation
Willing to not change pain treatments during study unless medically necessary.	major coexisting medical illness (e.g., cancer, COPD, morbid obesity)
Have not practiced yoga $> 2x$ in the last 3 months	Positive Romberg test (with or without sensory neuropathy)

Multimedia Appendixes

Peer-review.

URL: <http://asset.jmir.pub/assets/2465d478a5af47f8e59687ef2f4e5f4d.pdf>

Informed Consent Form.

URL: <http://asset.jmir.pub/assets/c5c9a9e8c86242e3a14ba1f4ecda8172.pdf>

