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Protocol for The Impact of CBT for Insomnia on Pain Symptoms and Central Sensitization in Fibromyalgia: A Randomized Controlled Trial

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ABSTRACT

Introduction: Approximately 50% of individuals with fibromyalgia (a chronic widespread pain condition) have comorbid insomnia. Treatment for these comorbid cases typically target pain, but growing research supports direct interventions for insomnia (e.g., Cognitive Behavioral Treatment for Insomnia, CBT-I) in these patients. Previous research suggests sustained hyperarousal mediated by a neural central sensitization mechanism may underlie insomnia and chronic pain symptoms in fibromyalgia. The proposed trial will evaluate the effects of CBT-I for not only reducing sleep, but also improving clinical pain and reducing central sensitization. The trial will be the first to evaluate the short and long-term neural mechanisms underlying insomnia and pain improvements in fibromyalgia.

Methods & Analysis: Female participants (N=130) 18 years of age and older with comorbid fibromyalgia (with pain severity of at least 50/100) and insomnia will be recruited from the University of Missouri in Columbia, MO, and surrounding areas. Participants will be randomized to 8 weeks (plus 4 bimonthly booster sessions) of CBT-I or a Sleep Hygiene control group (SH). Participants will be assessed at baseline, post-treatment, 6 and 12-month follow-ups. The following assessments will be completed: 2 weeks of daily diaries measuring sleep and pain, daily actigraphy, insomnia severity index, pain-related disability, single night of polysomnography recording, arousal (heart rate variability, cognitive affective arousal), structural and functional magnetic resonance imaging to examine pain-related neural activity and plasticity, and mood (depression, anxiety).

Ethics & Dissemination: Ethics approval was obtained in July 2018 from the University of Missouri. All data is expected to be collected by 2022. Full trial results are planned to be published by 2024. Secondary analyses of baseline data will be subsequently published.

Clinical Trial Registration Number: NCT03744156

STRENGTHS AND LIMITATIONS OF THIS STUDY

- 8-week Cognitive Behavioral Therapy for Insomnia integrates sleep education, hygiene, stimulus control, sleep restriction, relaxation, and cognitive restructuring techniques and will be examined relative to an active sleep hygiene (SH) control in patients with comorbid fibromyalgia and insomnia.
- Pain severity cutoff criteria maximizes potential to observe clinical and neural pain-related improvements following CBT-I.
- Investigation of neural pain mechanisms underlying effects of CBT-I relative to an active control will further understanding of central mechanisms underlying sustained pain in fibromyalgia.
- 6 and 12-month follow-up will enable examination of persistence of behavioral and neural outcomes of CBT-I.
- Potential limitations include participant attrition at follow-up, which may contribute to selection bias associated with systematic differences between participants completing CBT-I versus SH.

INTRODUCTION

Background

Chronic pain imposes a substantial public health burden, afflicting over 100 million Americans, with annual costs estimated at over $500 billion.[1] Individuals with chronic pain consume more health care services, yet 40% report inadequate management of their pain.[2] Chronic insomnia (at least 3 months of difficulty initiating and/or maintaining sleep, early morning awakening, or nonrestorative sleep)[3] is highly comorbid with pain, affecting at least 50% of chronic pain patients.[4] Recent research suggests chronic insomnia can lead to the development or worsening of chronic pain.[5] Thus, research efforts to prevent, and treat chronic pain should consider sleep disturbance as a primary intervention target.[5]

The relationship between fibromyalgia (a chronic condition characterized by widespread pain) and sleep disturbance is well established (e.g., see Harding's 1998 review[6]). Research on fibromyalgia has linked reports of restful sleep with less reported discomfort and fatigue,[7] and nonrestorative sleep with exacerbation of pain.[8] Polysomnographic studies have identified sleep architecture differences in fibromyalgia patients versus healthy controls (i.e., increased sleep onset latency,[9] lighter sleep,[9 10] more arousals,[11-13] reduced deep sleep[9 11 12]). More than 50% of persons with fibromyalgia meet insomnia criteria,[14 15] and fibromyalgia diagnostic criteria were recently revised to include sleep disturbance as a core feature.[16] The causal role of sleep in the etiology of chronic pain has gained empirical support.[17 18] Longitudinal, experimental, and trial evidence over the past decade suggest sleep may be a more reliable predictor of chronic pain, than vice versa.[5 19] When chronic pain and insomnia co-occur, treatment typically focuses on pain. The insomnia is considered a symptom and thus, is expected to improve following improvement in pain. However,

a growing body of research,[5] including our recent trial,[20] supports direct intervention for insomnia in the context of pain.

Fibromyalgia is characterized by chronic widespread pain, central sensitization (CS) and mechanical allodynia.[15] The predominant pathophysiology of pain in FM is abnormal central pain processing or CS.[15] CS is characterized by increased responsiveness of the central nervous system (CNS) to noxious and non-noxious stimuli. Hyperalgesia and allodynia, important consequences of CS, are related to increased excitability of spinal and supraspinal neurons.[21] Patients with fibromyalgia have a higher rate of temporal summation of heat-evoked second pain (TSSP), a proxy for CS, compared to pain-free controls.[21] TSSP (aka wind-up) and subsequent aftersensations are greatly prolonged in FM.[21] Importantly, mechanical allodynia, enhanced wind-up, and prolonged aftersensations represent CS features found to be relevant predictors of fibromyalgia clinical pain.[22]

The Cognitive Activation Theory of Stress (CATS) posits chronic arousal leads to changes in the CNS consistent with CS.[23] CATS provides a framework illustrating the mechanisms by which CBT-I can improve pain. CATS proposes that through chronic arousal and insomnia (which has been linked to arousal – as described below), there are critical changes to hypothalamic-pituitary-adrenal (HPA) and CNS functioning that prompt increased sensitivity to stimulation, particularly pain.[23] We propose CBT-I improves pain by reducing arousal and improving sleep; thereby, reversing the negative HPA and CNS changes (i.e., reversing CS) that sustain chronic pain. Cognitive factors are key contributors to arousal in CATS and have a strong empirical basis to support their relationship to insomnia and chronic pain.[7 24] Chronic arousal and poor sleep, via their effects on the nervous system, are plausible candidates for explaining the relationships of

cognitive states (catastrophizing, somatic focus) and ongoing nociceptive input[8] to CS and chronic pain.

Hyperarousal is a well-established maintenance factor of chronic insomnia.[55] Persons with insomnia often develop increased cognitive focus and catastrophizing cognitions (e.g., "I will never sleep well again.") that increase arousal and interfere with getting good sleep. Cognitive therapy (a component of CBT-I) effectively targets and replaces such thoughts (e.g., "Everyone sleeps poorly on occasion."); thereby, reducing cognitive arousal and improving sleep. Previously, we found CBT-I produced large, significant improvements in sleep- and pain-related cognitive-affective arousal.[20] However, because arousal is a multidimensional construct, we have included multiple measures in the present trial – cognitive [non-specific (perceived stress), condition specific (dysfunctional sleep cognitions, pain catastrophizing)] and peripheral (heart rate variability, HRV). In terms of peripheral arousal, studies have found alterations in heart rate (HR) and heart rate variability (HRV) while awake before sleep and during Stage-2 non-REM sleep,[25] increased low frequency power and decreased high frequency power across all sleep stages,[26] and lower wake-to-sleep HR reduction and standard deviation of RR intervals (SDNN),[27] in persons with chronic insomnia compared to controls, consistent with increased sympathetic activity. An uncontrolled study in patients with primary insomnia found alterations of HRV following CBT-I.[28] Given our theoretical framework that CBT-I will prompt a reduction of arousal, we expect a decrease of sympathetic activity (i.e., increase in HRV) at post-treatment and both follow-ups in the proposed study.

Pain is multidimensional and evidence indicates different brain regions,[29] CNS pathways,[30] and functional interactions[31] are dynamically involved in creating the subjective pain experience. Research has identified changes in neural activity in a variety of brain regions that are positively

correlated with pain.[32 33] These regions comprise various neural networks involved with processing different dimensions of the pain experience: parts of medial and posterior thalamus, somatosensory cortices (S1/S2), insular cortical areas (posterior, mid, anterior insula), cingulate cortical areas (subgenual and pregenual anterior cingulate, anterior midcingulate, posterior cingulate), caudate/putamen, and cerebellar areas. The purpose of neuroimaging in the current trial is to increase knowledge of the underlying neural mechanisms associated with chronic pain and how to manipulate them to treat chronic pain by targeting insomnia. Consistent with CATS,[34] our fMRI results suggest chronic pain may result from abnormal pain modulation processes. In our previous imaging work, results indicated aberrant pain processing seen in fibromyalgia is due to sustained arousal across common pain processing networks.[35 36] Moreover, we identified treatment related changes in neural activity among brain regions involved in the cognitive and affective dimensions of pain.[31 37]

Fibromyalgia is associated with gray matter atrophy in the amygdala, cingulate, insula, medial frontal cortex, parahippocampus, and prefrontal cortex.[18 38-40] Neuroimaging research has also been associated chronic insomnia with reduced gray matter in the amygdala, orbitofrontal cortex, and precuneus.[41 42] Of particular interest, several studies have examined the Default Mode Network (DMN) and found both fibromyalgia[43 44] and insomnia[45 46] are characterized by heightened activity and connectivity patterns not typically observed in healthy persons. The present trial will be the first to examine CBT-I's impact on the DMN in patients with fibromyalgia and comorbid insomnia.

The efficacy of CBT-I is well established. The vast majority (~70-80%) of persons with insomnia treated behaviorally show sleep improvements that maintain through follow-ups up to 2 years, and patients rate behavioral techniques as more acceptable than sleep medications.[17] Unlike

sleep medications, behavioral approaches do not pose serious side effects and may be more cost effective in the long-run.[47] A meta-analysis[48] of non-pharmacological interventions for insomnia (all involved at least one component of CBT-I) in chronic pain patients (11 RCTs, 3 involving fibromyalgia) found large sleep quality improvements and small to moderate pain reductions following treatment. Sleep quality effects were maintained at 1 year. To date, most CBT-I trials in chronic pain patients,[48] and the two CBT-I trials in fibromyalgia[49 50] have not required a specific minimum level of pain severity for inclusion. Thus, it is possible that individuals with low levels of pain were included in these trials and did not have high enough initial pain severity to show substantial improvement.

The proposed trial examines the novel hypothesis that sustained improvements in arousal, sleep, and CS will result in sustained (or possibly enhanced) pain improvements over time. Currently, the long-term effects of CBT-I on clinical pain and its underlying neural mechanisms in FM are unknown. The proposed trial offers the following methodological improvements: 1) recruitment of participants with more severe baseline pain, 2) expanded arousal outcomes (peripheral arousal, global cognitive arousal/stress, sleep- and pain-related cognitive-affective factors), 3) imaging follow-ups at 6 and 12 months, 4) booster sessions (to ensure long-term maintenance of treatment effects), 5) a credible active control–sleep hygiene (to control for attentional/nonspecific therapeutic effects), and 6) inclusion of moderation/mediation analyses. The proposed trial addresses key shortcomings in our current understanding of chronic pain.

Aims

The overarching goal of this randomized controlled trial is to study the temporal relationships between our hypothesized mediators and pain. In our recent trial, CBT-I prompted larger initial improvements in sleep[20] and CS[51] than did CBT-P. Given sleep and CS's

hypothesized mediating roles, we focus on CBT-I only here. Our first specific aim is to examine the effects of eight weeks of CBT-I relative to eight weeks of sleep hygiene control (SH) on arousal (heart rate variability, cognitive-affective-dysfunctional sleep and pain cognitions, perceived global stress), subjective/objective sleep (sleep onset latency, wake after sleep onset, sleep efficiency and quality; insomnia impact), pain after treatment and at 6 and 12 month follow-ups. Our second specific aim is to examine CBT-I's effect on resting state brain activity as well as neural activation patterns of functional brain networks and Blood-Oxygen-Level Dependent (BOLD) responses to painful stimuli in regions associated with pain processing. Our third specific aim is to study CBT-I's long-term effect on structural characteristics of pain-related brain regions. Finally, our fourth aim is to examine the mediating impact of arousal, sleep, and CS on pain.

METHODS

Trial Design and Study Setting

Female patients (18 years of age and older) with fibromyalgia and chronic insomnia will be recruited from the University of Missouri in Columbia, MO, and surrounding area. Participants will be recruited through physician referral from Rheumatology, Internal Medicine and Sleep Clinics as well as community advertisements. Participants will be randomized to 8 weeks of CBT-I or sleep hygiene (SH). Both groups will receive 4 bimonthly phone booster sessions (B; See Figure 1). Baseline, post-treatment, and 6 and 12 month follow-ups will measure sleep, arousal, neural plasticity, and pain. All participants will sign written informed consent. Participants will be compensated $150 following the baseline, post-treatment, 6 and 12 month follow-up assessments. All procedures were approved by the University of Missouri Institutional Review Board on July 11th 2018.

Eligibility Criteria

Inclusion criteria are: 1) female, 2) 18+ years of age, 3) willing to be randomized, 4) can read and understand English, 5) diagnosed with fibromyalgia [a) pain for 6+ months that is b) confirmed by tender point test (with application of 4kg force, participant reports pain in at least 11 of 18 points, including points in all four body quadrants,[15] and c) baseline diaries indicate average pain intensity of ≥50/100] and insomnia [a) insomnia complaints for 6+ months that b) occur despite adequate opportunity and circumstances for sleep, and c) consist of 1 or more of the following: difficulty falling asleep, staying asleep, or waking up too early, d) daytime dysfunction (mood, cognitive, social, occupational) due to insomnia, e) baseline diaries indicate >30 minutes of sleep onset latency or wake after sleep onset on 6 or more nights], 6) no prescribed or over the counter pain or sleep medications for 1+ month, or stabilized on medications for 6+ weeks.

Exclusion criteria are: 1) unable to provide informed consent, 2) cognitive impairment (Mini-Mental State Examination <26), 3) sleep disorder other than insomnia [i.e., sleep apnea (apnea/hypopnea index, AHI >15), Periodic Limb Movement Disorder (myoclonus arousals per hour >15)], 4) bipolar or seizure disorder (due to risk of sleep restriction treatment), 5) other major psychopathology except depression or anxiety (e.g., suicidal ideation/intent, psychotic disorders), 6) severe untreated psychiatric comorbidity, 7) psychotropic or other medications (e.g., beta-blockers) that alter pain or sleep, 8) participation in non-pharmacological treatment (including CBT) for pain, sleep or mood outside current trial, 9) internal metal objects or electrical devices, 10) pregnancy.

Randomization

Biostatistician (C.D.) will select block size and perform randomization. Other personnel (except for therapists and project coordinator) will be blinded to randomization. Blocking guarantees balance, increases power,[52] and will be accounted for in analyses.

Procedures

Screening

Screening to assess fibromyalgia and insomnia symptoms and to rule out sleep disorders other than insomnia is carried out in four stages:

Stage 1: Brief Screener (~10 mins). The project coordinator will conduct a brief structured interview to address inclusion/exclusion criteria and establish probable FM and insomnia diagnoses.

Stage 2: Clinical Interview (~50 mins). The assessor will: 1) conduct a semi-structured pain, sleep, and psychiatric interview, 2) perform tender point testing. Diagnosis of fibromyalgia will be overseen by a rheumatologist (R.S.).

Stage 3: Polysomnography (PSG; 1 overnight). One night of polysomnography will rule out sleep disorders other than insomnia (i.e., apnea, PLMD). The assessor will prepare participants for PSG in their own homes, and participants will sleep in their own beds. Referrals will be made for those disqualified to a neurologist (P.S.).

Stage 4: Sleep Diary Confirmation of Insomnia (~5 mins/day). Baseline sleep diaries will be used to confirm insomnia diagnosis and must show: >30 minutes of sleep onset latency or wake after sleep onset on 6+ nights during the 2 weeks. Sleep diaries will be collected electronically via an online data management system (Qualtrics) with personal web-enabled devices or (if needed) study provided devices. Diagnosis of insomnia will be overseen by a sleep psychologist (C.S.M.).

Interventions

Both interventions include 8 weekly, 50 minute individual face to face sessions with a therapist (predoctoral graduate students in an APA accredited clinical or school psychology program at the University of Missouri) and 4 bimonthly, 20 minute phone booster sessions. SH will meet on the same schedule as CBT-I, controlling for therapist attention and other nonspecific therapeutic factors. Session content for CBT-I and SH are provided in Tables 1 and 2, respectively.

Treatment Integrity

Lichstein's[53] 3-step method will be used to measure Treatment Integrity.

1. Treatment Delivery/Training

Therapists will use manuals. Practice will begin with mock sessions and then recorded sessions with volunteers. The Principal Investigator (PI; C.S.M.) will score all training sessions. Training will last ~16 weeks until therapists obtain mastery (scoring 100 on each session's Treatment Delivery Score Sheet). For assessment of participant treatment delivery, all sessions will be recorded. Fifty percent will be scored by consultant (registered psychologist). Senior consultant (registered psychologist) will double score initial 10 treatment and 10 booster sessions to establish fidelity, and 10% of remaining sessions for reliability. Consultants will inform the PI of scores <95% for supervisory/training purposes. The PI will review 25% and therapists will review 25% of each other's sessions for ongoing training/supervision. Only consultant reviews will be used to assess fidelity.

2. Treatment Receipt

To ensure treatment comprehension, participants will be encouraged to ask questions. Workbooks describe and reinforce treatment content. To assess treatment receipt, participants will complete a brief quiz at end of Session 4.

3. Treatment Enactment

To ensure home assignments are done, workbooks contain written instructions on home assignments. To assess enactment, participants will maintain daily electronic diaries and logs.

Treatment Credibility and Expectancy

At the end of Session 3, participants will complete a treatment credibility questionnaire. This 4-item scale assesses the participant reaction to therapist and treatment efficacy, and participants provide ratings of 1 (strongly disagree) to 10 (strongly agree). Higher scores represent better treatment credibility. At the end of session 3 therapists will complete an expectancy for improvement scale.

Outcomes

A summary and timeline of study outcomes are provided in Tables 3 and 4.

Study Timeline

The study timeline is provided in Table 5.

Data Analysis

Power Analysis

Effect sizes in our prior trial that were small to medium for pain (*f*=.2), medium to large for sleep (*f*=.31-39), large for imaging (*f*=.69-1.13), and large for pain- and sleep-related cognitive-affective arousal (*f*=.69-1.13). To ensure adequate power with an active control, effect sizes from CBT-I trials in fibromyalgia with SH control groups were considered and ranged from small to medium for pain (*f* =.15-.25; including pain-related anxiety) and small to large for sleep outcomes (*f*=.15-.40).[3,4] Our prior trial did not measure peripheral arousal. However, based on prior research,[7] small to medium effects (*f*=.15-.25) are expected. Using G-Power[54] for RM ANOVA within-between interaction, setting α=.05, number of groups=2, number of measurements=4, and

correlations between repeated measures=.5, minimum statistical power=.8, the sample size required to detect a small effect of f =.15 is 62. For the mediation model tested in Aim 4, given that the ESs of the mediating paths range from small to large (f=.15 to .40), a sample size of 130 provides sufficient power (>.8) to detect the mediation effects on pain.[55]

Missing Values

To account for missing outcome values, 3 steps will be followed: 1) group dropout rates will be compared using chi-square analyses to assess for systematic differences, 2) demographic and dependent variables will be examined for relationship to dropout. Related variables will be used to impute missing values for use in analyses below (via SPSS Missing Items Analysis), 3) completers vs. imputated analyses wil be compared to further estimate dropout effects.

Image Analysis

Programs such as SPM and FSL will be used to analyze the imaging data. Standard pre-processing steps will minimize physiological and motion related artifacts. Data will be warped into a standardized stereotaxic space (i.e., Montreal Neurologic Institute). Individual level whole brain analyses will produce statistical parameter maps (*SPMs*) associating each voxel's neural activation pattern to the experimental protocol, which will then be used in group-level analyses. Type-I error precautions include: repeated measures correction, p<0.05 for the false discovery rate (FDR) and family wise error (FWE) corrections. Significant clusters will have: 50+ contiguous voxels, volume≤100 µL, and be located in conceptually relevant regions. These parameters establish an image-wise p of .00002 and effective pixel-wise alpha of p < .0002.[56]

Diffusion Weighted Imaging (DWI).

DWI data measures the diffusion of water across cell membranes in 3D. Because the data are collected in three-dimensional space, the directionality of the diffusion, called anisotropy, can

be determined. Diffusion Tensor Imaging (DTI) is a technique for measuring anisotropy with DWI data. SPM and FSL will provide information about the apparent diffusion coefficient (ADC), and fractional anisotropy (FA). ADC is how much diffusion is possible (independent of orientation). FA is an index of diffusion directionality; values range from 0-1 (0=isotropic diffusion; 1=diffusion in a single direction). Higher values of FA and reduced ADC represent increased complexity of brain tissue.[57 58] Conversely, chronic pain/sleep-related abnormalities of the white and gray matter should decrease FA and increase ADC.[57 58] Probabilistic tractography uses DWI data to map fiber tracts and identify/model anatomic connections among brain regions.[40 59 60]

Targeted Brain Regions

Brain regions routinely involved in pain and its modulation will be regions of interest, including the somatosensory cortices, cingulate cortices (anterior, mid-dorsal), dorsolateral prefrontal cortex, frontal gyri (superior, middle, inferior), insula (anterior, posterior), temporal gyri, thalamus, and periaqueductal gray.[35 36 61-64]

Evaluation of Aims

To examine the effects of CBT-I on arousal, sleep, and pain in fibromyalgia patients (Aim 1)**,** we will use a series of RM ANOVAs. Group (CBT-I, SH) will serve as a between subject factor, while time (baseline, post-treatment, 6 months, 12 months) will serve as a within-subject factor. Based on a priori hypotheses, separate ANOVAs (GLM) will be conducted for each sleep, arousal, and pain outcome. Planned contrasts will be conducted consistent with a priori hypotheses. Because we have specific a priori hypotheses about each variable representing specific components/mechanisms, our analytic approach is based primarily on univariate (ANOVA) analyses. Univariate ANOVAs will help maintain high sensitivity and specificity, which is important because: 1) there are specific treatment implications for each outcome, and 2), univariate

analyses are most compatible with previously published research. Multi-collinearity will be assessed. Based on degree of collinearity, MANOVA's with step-down F-tests will be conducted to determine relative importance of each variable to group differences. Based on our recent trial analyses, linear and polynomial trends will be examined.

To examine CBT-I's effect on resting state brain activity as well as neural activation patterns of functional brain networks and Blood-Oxygen-Level Dependent (BOLD) responses to painful stimuli in regions associated with pain processing (Aim 2), we will use several neuroimaging analysis methods. The functioning of the DMN, including response to treatment, will be assessed via independent component analyses (ICA) using the GIFT toolbox. Independent Component Analysis (ICA) is a technique for decomposing in time-series data (e.g., fMRI) into a set of orthogonal components from a known source of mixed signals GIFT toolbox and produces a spatial map of brain regions (i.e., a network) that share a particular component. By comparing the component representative of the DMN for each group to a DMN template, we can make statistical inferences about group related differences and treatment related changes over time. Group related differences in BOLD activity for each scanning session will be assessed using a random effects general linear model (RFX-GLM) and RM ANOVA. These analyses will identify group and group by time differences in neural response to painful thermal stimulation, and identify brain regions in which neural activity is sensitive to treatment. Additionally, RM ANOVA will allow for the examination of behavioral covariate influences on outcomes.

To study CBT-I's long-term effect on structural characteristics of pain-related brain regions (Aim 3), we will use the program FSL tissue segmentation pipeline. This program has automated procedures for volumes of gray and white matter and thickness of the cortical ribbon. Additionally, it has a built-in algorithm for identifying longitudinal changes in the aforementioned

measurements. As with a RM ANOVA, the algorithm accounts for the inherent auto correlations in the data due to repeated sampling. Thus, we will be able to assess whether the relationship between measures of arousal, sleep, pain, and gray matter thickness, in regions of interest (ROIs) between groups at each measurement interval, changes over time. Analytic approaches for hypothesized non-linear patterns are established and more easily interpreted using GLM; however, MLM approaches will be used if their advantages increase.

Finally, to examine the mediating impact of arousal, sleep, and CS on the effects of CBT-I on pain (Aim 4), we will use 4-wave cross-lagged path analysis. Controlling for baseline, autoregressions, and reciprocal effects among sleep, arousal (HRV, cognitive arousal, stress), and CS (neural factors), we will examine whether CBT-I continues to predict improved sleep and decreased arousal and CS at 6 mos, and then predicts pain at 12 mos. Mediation effects of arousal, CS, and improved sleep of impact of CBT-I on pain outcomes at 12 months will be estimated. We will evaluate whether mediation effects remain significant after controlling for global and pain- and sleep-specific cognitive-affective variables.

Ethics and Dissemination

All study procedures were approved by the Institutional Review Board at the University of Missouri on July 11th 2018. An independent 4 member Safety Monitoring Committee (SMC) was assembled in January 2019 to oversee the study. Members include those with expertise in fibromyalgia, chronic insomnia, sleep medicine and CBT. All SMC members attested that they have no conflicts of interest. The SMC met once via conference call at the beginning of the study to review the study protocol, Manual of Operating Procedures (MOOP), Informed Consent Form, and monitoring plan with emphasis on data integrity and patient safety issues. Following this initial meeting, the SMC will meet every 6 months to review progress reports prepared by the team

biostatistician. Those SMC reports will include interim statistical analyses. Any changes to these procedures that are recommended by the SMC will be adopted. The SMC will review adverse events and monitor study results, focusing on efficacy, recruitment progress, randomization, compliance, retention, protocol adherence, operating procedures, forms completion, intervention effects, participant safety, and minority inclusion. The PI registered the study within ClinicalTrials.gov (NCT03744156) on November 16th, 2018. The PI will also submit annual reports to the funding agency.

Results from this trial will be presenting at national conferences, including the Associated Professional Sleep Societies (APSS or SLEEP) and the American Pain Society, in the final year of the project. Dissemination will also occur through the submission of a primary article on the outcomes, a second article focusing on the functional neural changes (i.e., resting state and fMRI results), a third article focusing on the structural neural changes, and a fourth focusing on outcome mediation. The treatment materials will be shared electronically and will be widely available to clinicians.

Table 1. Session Content for CBT-I

Session Number	Content
1. Sleep Education	Participants will be provided with education on sleep stages; sleep and fibromyalgia; and circadian rhythms and sleep. This information is given to provide a heuristic background for the specific sleep techniques used.
2. Sleep Hygiene (SH)	SH will be discussed and participants are instructed to adhere to the following rules: 1-Avoid caffeine after noon, 2-Within 2 hours of bed, avoid exercise, nicotine, alcohol, and heavy meals, 3-Within 1 hour of bedtime, avoid screen time. The goal of SH is to eliminate sleep-interfering behaviors.
3. Stimulus Control (SC) & Brief Relaxation	SC will be discussed and participants will be asked to adhere to the following recommendations: 1-Do not use bed/bedroom for anything but sleep (or sex), 2-If not asleep in 15-20 mins, leave bed, do something non-arousing in another room. Return to bed when sleepy. If not asleep in 20 mins, repeat., 3-If awake & not back asleep in 20 mins, repeat #2, 4-Avoid napping. The goal of SC is to break incompatible/build compatible sleep associations. In addition, a 10 min relaxation exercise will be recorded and given to participants for practice at bedtime & once during the day. The goal of this is to induce relaxation/reduce arousal.
4. Sleep Restriction	A time in bed prescription (Rx) will be set at baseline average diary reported total sleep time plus 30 mins. If this value is <5 hrs, Rx will be set at 5 hrs. The therapist and participant will work together to set regular bed/wake times consistent with Rx. The goal of sleep restriction is to regulate sleep-wake cycle and reduce awake time in bed.
5. Monitoring Automatic Thoughts	Thoughts, thought patterns and emotional reactions that interfere with getting good

	sleep (i.e., “I will never sleep well again.”) will be identified and monitored.
6. Challenging/Replacing Dysfunctional Thoughts	The validity of sleep-interfering thoughts will be challenged and replaced with sleep conducive ones (i.e., “There are things I can do to improve my sleep.”)
7. Practical Recommendations	Established cognitive restructuring techniques (i.e., reappraisal, reattribution, and decatastrophizing) will be taught.
8. Review and Maintenance	Learned skills and importance of a regular sleep schedule and good sleep habits will be reviewed. Continued use of the techniques learned will be discussed.
Booster Sessions	In this brief (~20 mins) telephone session, techniques from Session 1-8 will be reviewed. The therapist will encourage continued practice of techniques. Problems will be trouble-shooted.

Table 2. Session Content for SH

Session Number	Content
1. Sleep Education	Content is the same as CBT-I
2. Sleep Hygiene (SH)	Content is the same as CBT-I.
3. Insomnia and Pain	Participants are provided education on chronic/acute insomnia (Spielman's 3 P's Model)[53] and the Gate Control Theory[54] of Pain.
4. Environment	Participants are provided with education on SH rules related to environmental factors (e.g., noise, light).
5. Lifestyle	Participants are provided with education on lifestyle factors that influence sleep (e.g., use of stimulants & other substances).
6. Diet	Participants are provided with education about diet and nutrition and their influence on sleep.
7. Exercise	Participants are provided with education about exercise and its influence on sleep.
8. Review and Maintenance	In the final session, SH training reviewed and continued practice is encouraged. Problems are trouble-shooted. All education provided in previous sessions will be reviewed. Finally, continued engagement in education will be discussed.
Booster Sessions	As in CBT-I, all training and education covered in SH training will be reviewed in a brief (~20 mins) telephone call. Continued SH practice and education engagement are encouraged. Problems are trouble-shooted.

Table 3. Outcome Measures

Outcome Category	Measure	Primary/Secondary	Details
Subjective Sleep	Daily Sleep Diaries	Primary	Online diaries will be completed each morning (~5 mins) during each 2 week assessment period and 8 weeks of treatment. Primary outcome variables include: sleep onset latency (SOL; time from initial lights-out until sleep onset), wake after sleep onset (WASO; time awake after initial sleep onset until last awakening), number of awakenings, total sleep time, sleep efficiency (total sleep time/time spent in bed × 100), and sleep quality rating (1-very poor to 7-excellent). Sleep and pain medication consumption variables will include: name, dosage, and time taken. Sleep medication will be converted to number of lowest recommended dosage (LRD) units,[65] and pain medication to morphine equivalent dosage (MED).[66]
	Insomnia Severity Index (ISI)	Primary	At each time point, participants will complete the ISI (primary outcome).[67] The ISI is a seven item questionnaire that assesses the frequency and/or severity of insomnia symptoms [e.g., "rate the current severity of your difficulty falling asleep"; choices range from 0 (none) to very severe (5)], as well as questions regarding the impact of insomnia on daytime functioning [e.g., "to what extent do you do you consider your sleep problem to interfere with your daily functioning (e.g. daytime fatigue, mood, ability to function at work/daily chores, concentration, memory, mood, etc.) currently?; choices range from 0 (not interfering at all) to 5 (very much interfering). Total scores on the ISI range from 0-28, with higher scores representing more severe insomnia.
Objective Sleep	Daily Actigraphy	Secondary	Actiwatch 2® (Philips Respironics) is a watch-like device that monitors light and gross motor activity. Data will be analyzed by proprietary software using 30s epochs. A validated algorithm estimates the same variables (secondary outcomes) provided by diaries (except sleep

			quality). Participants wear the device 24/7 during each 2 weeks of assessment, and 8 weeks of treatment.
	Polysomnographic Sleep	Secondary	The Comet-PLUS® Portable (Natus Neurology) Recording System will be used to conduct a single in-home overnight sleep study at baseline, post-treatment, and both follow-ups. Consistent with ambulatory recommendations,[68] monitoring consists of 10 EEG, 2 EOG, and 3 EMG (chin) using standard placement. It also includes respiratory inductance plethysmography (thoracic/abdominal effort), oximeter (pulse/oxygen saturation), electrocardiogram (ECG), R/L anterior tibialis EMG, oral-nasal airflow thermocouple, and nasal cannula pressure transducer. We require 4 hrs of acceptable data (i.e., scorable stage/respiratory events) and follow Sleep Heart Health Study (SHHS)[94] procedures for training, data management, and scoring. PSG provides sleep stage % (stage 1, 2, 3, Rapid Eye Movement Sleep) and absolute values for diary variables (secondary outcomes).
Arousal	Peripheral Arousal – Heart Rate Variability (HRV)	Primary	Using Holter monitors, we will obtain 5 minute electrocardiogram recordings during rest in a quiet controlled environment at each assessment. Time and spectral analysis of the short-term variability of HR will be performed using Pathfinder (Spacelabs, Seattle, WA) software to assess the neural regulation of HR. The time domain indices reflect the beat-to-beat variability with respect to time. The variables standard deviation of the N-N intervals (SDNN) and the percentage of N-N intervals that exceed 50 ms (pNN50) will be examined. The frequency domain indices reflect the underlying rhythms of the mechanisms modulating heart rate. High frequency (0.15-0.4 Hz), low frequency (0.04-0.15 Hz), and very low frequency (below 0.04 Hz) spectral bands will be examined.
	Global Cognitive Arousal-Perceived Stress Scale (PSS)[96]	Primary	The PSS (primary outcome) is a 10 item questionnaire that asks participants to appraise their stress level during the past month in response to several everyday situations (e.g., "in the last month how

			often have you been able to control irritations in your life?"). Choices range from 0 (never) to 4 (very often). Higher total scores on the PSS indicate worse perceived stress.
	Insomnia-Specific Cognitive-Affective Arousal - Dysfunctional Beliefs and Attitudes about Sleep (DBAS)	Primary	The DBAS[67] is a 28 item scale that assesses the degree to which an individual agrees with statements regarding sleep (e.g., "Medication is probably the only solution to sleeping", "I need 8 hours of sleep to feel refreshed and function well during a day"). Participants rate their belief in each statement from 0 (strongly disagree) to 10 (strongly agree). Scores for each item are summed and higher scores on the DBAS indicate worse cognitive affective arousal related to insomnia.
	Pain-Specific Cognitive-Affective Arousal-Catastrophizing-Pain Catastrophizing Scale (PCS)[69]	Primary	The PCS is a 13-item scale that measures the degree (from 0-not at all to 4-all the time) to which participants experienced certain thoughts or feelings during past painful events. Items are scored and total scores on the PCS represent worse pain catastrophizing.
Pain	Daily Clinical Pain-Electronic Daily Diaries	Primary	On the daily electronic diaries, participants provide ratings on a 0-100 scale regarding their pain intensity (0-no pain sensation, 100-most intense pain imaginable) and pain unpleasantness (0-not at all unpleasant, 100-most unpleasant imaginable).
	Subjective Pain-McGill Pain Questionnaire (MPQ)[70 71]	Secondary	The MPQ assesses participants pain symptoms across 21 categories. For each category, participants select the best word that described their pain. Qualitative responses are coded by numerical value (e.g., 1-3 or 1-5), with higher values representing worse pain in that category. If they do not experience a specific category of pain, they do not provide a response to that category. Category scores are summed and total scores could range from 0 (no pain) to 78 (severe pain).

	Patient-Centered Outcomes Ques. (PCOQ)[72]	Secondary	The PCOQ is a 5-item questionnaire that assess on a 0-10 point scale usual levels of pain, desired levels of pain, what level of improvement in treatment outcomes they would consider successful, what level of improvement in treatment outcomes they expect after treatment, importance of improvement in treatment outcomes.
	Pain-Related Disability-Pain Disability Inventory (PDI)[73 74]	Secondary	The PDI includes 7-items rated on an 11-point scale (0 = no disability, 10 = total disability) indicating the degree to which chronic pain interferes with participant functioning in the following areas: family/home responsibilities, recreation, social activity, occupation, sexual behavior, self-care, and life-sustaining activity. The seven ratings are summed to compute a total score (0-70), with higher scores indicated worse pain disability.
Mood	State Trait Anxiety Inventory (STAI)[75]	Covariate	STAI asks respondents to rate how true 20 self-descriptive statements (e.g., I feel calm) are on a 4-point scale (1 = not at all, 4 = very much so). Typically, respondents are asked to rate statements according to how they generally feel (trait-anxiety scale) and how they feel in the current moment (state-anxiety scale). Total scores range from 20 to 80, with higher scores indicating greater maladjustment.
	Beck Depression Inventory – 2nd Edition (BDI-II)[76]	Covariate	The BDI-II contains 21 items that measure the severity of depressive symptomatology on a three-point scale (0 = absence of symptoms, 3 = most severe). Typically, respondents answer for the previous week, but the previous two weeks were used in this study to match the two-week activity recording period for each assessment. Total scores range from 0 to 63. Ranges for clinical levels of depression are 0 to 13 (minimal), 14 to 19 (mild), 20 to 28 (moderate), and 29 to 63 (severe).
	Pain Anxiety Symptoms Scale (PASS-20)[77]	Covariate	The PASS measures fear and anxiety responses related to pain. The PASS-20 revised short form version contains 20 items in which participants must rate the frequency in which they experience fearful and anxiety ridden responses related to pain or pain-related situations.

			This scale is widely used in clinical screening of chronic pain and pain research.
	Anxiety and Preoccupation about Sleep Questionnaire (PSQ)[78]	Covariate	The APSQ measures the intensity of both daytime and nighttime worry related to insomnia. Participants are presented with 10 statements describing several sleep related worries and participants are asked to indicate how true they on a scale from 1 (not true) to 10 (very true). Scores on this scale are associated with self-reported (e.g., diary) sleep measures as well as daytime impairment, with higher scores representing worse anxiety related to sleep.
Neuroimaging	Noxious Thermal Stimuli-Temporal Summation of Second Pain (Wind-up)	Primary	Three imaging protocols, 1) structural MRI (MPRAGE), 2) functional MRI (EPI BOLD), and 3) Diffusion Weighted Imaging (DWI), will assess neural plasticity. A Siemens 3.0 T research dedicated scanner with a 32-channel head coil will be used. Scanning session lasts 1 hour or less. First, structural scan lasts ~5 min. followed by 5 functional MRI scans lasting ~25 mins (2 resting state, 3 experimental pain scans, each 5 min.), and then Diffusion Weighted Imaging scan (~12 mins). During each 5 min. pain scan, participants are exposed to 3 trains of Wind-up and 8 RH stimuli (See above). Each train is followed by at least 30s of rest while the 8 RH stimuli are followed by an average of 10s of rest.
	Noxious Thermal Stimuli-Graded Thermal Stimulation or RAMP and HOLD (RH)	Secondary	To look at pain-related brain activity, a computer-controlled Medoc Pain and Sensory Evaluation System (Pathway Model ATS, Medoc Advanced Medical Systems, Durham, NC) will be used to deliver thermal stimuli through a contact thermode to the plantar foot surface while participants are in the scanner. Temperature levels will be monitored by a contactor-contained thermistor and return to baseline of 32˚ C at an active cooling rate of 10˚ C/Sec. To mitigate sensitization, the thermode will be moved to opposite foot at each cycle end. Test site sequence will be determined by random number generator, using select without replacement option. Visual Analogue Scale (VAS) ratings

	from 0 (no pain) to 100 (worse pain imaginable) will be obtained following each run.

Table 4. Schedule of Outcome Measures

Assessment Period	Base	Tx	Post	Boosters	FUs
Weeks	**2**	**8**	**2**	**2**	**2**
Telephone & clinical interviews, consent, MMSE	X				
Actigraph, PSG, ISI, MPQ, PDI, RH, Wind-Up, HRV, DBAS, PSS, PCS, STAI, BDI-II, PASS-20, APSQ	X		X		X
Electronic Daily Diaries	X	X	X	X	X
Tx Integrity – Delivery & Receipt, Treatment Credibility		X			

Note. MMSE = Mini Mental State Examination; PSG = Polysomnography; ISI = Insomnia Severity Index; MPQ = McGill Pain Questionnaire; PDI = Pain Disability Inventory; RH = Ramp and Hold; HRV = Heart Rate Variability; DBAS = Dysfunctional Beliefs about Sleep Scale; PSS = Pain Severity Scale; PCS = Pain Catastrophizing Scale ; STAI = State Trait Anxiety Inventory; BDI-II = Beck Depression Inventory – 2nd Edition; PASS-20 = Pain Anxiety Symptoms Scale; APSQ = Anxiety and Preoccupation about Sleep Questionnaire

Table 5. Study Timeline

Project Year→	1		2		3		4		5	
Half →	1	2	1	2	1	2	1	2	1	2
1. Develop Manual of Operating Procedures. Register with clinicaltrials.gov. Publish trial protocol. Develop SH. Train therapists & assessor.	■									
2. Recruit, collect baseline, deliver treatment		■	■	■	■	■	■			
3. Collect post-treatment assessment							■	■		
4. Collect 6 & 12 month follow-up assessments			■	■	■	■	■	■		
5. Offer/provide CBT-I to SH controls									■	
6. Final data analysis & dissemination (continues after grant ends); final report									■	■

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Contributors

All authors made substantial contributions to the concept and design of the study. CSM drafted initial protocol, with input from all authors. JCG, RS, MR drafted MRI protocol. CBD drafted statistical analysis plan. CSM, PS and CS drafted screening procedures. CSM and AFC drafted the manuscript. All authors revised the manuscript.

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Disclaimer

The study sponsor was not actively responsible or involved in the study design and will have no involvement in collection, management, analysis or interpretation of data. The sponsor will have no involvement in future manuscript preparation and decision to submit for publication. This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Competing Interests

None declared.

Ethics approval

The study and methods were evaluated and approved by the Institutional Review Board at the University of Missouri (IRB Project Number: 2011835).

Provenance and peer review

Externally peer reviewed at the NINR at the NIH.

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List of Figures

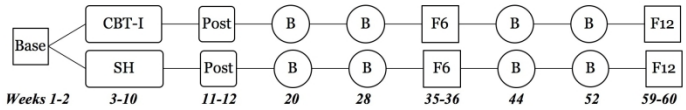

Figure 1. Timeline of Randomized Controlled Trial

215x279mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Check (x)	Description
			Administrative information
Title	1	x	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a	x	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	x	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	x	Date and version identifier
Funding	4	x	Sources and types of financial, material, and other support
Roles and responsibilities	5a	x	Names, affiliations, and roles of protocol contributors
	5b	x	Name and contact information for the trial sponsor
	5c	x	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	x	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction			
Background and rationale	6a	x	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	x	Explanation for choice of comparators
Objectives	7	x	Specific objectives or hypotheses

Trial design	8	x	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
			Methods: Participants, interventions, and outcomes
Study setting	9	x	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	10	x	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11a	x	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	x	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	x	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	x	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12	x	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	13	x	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14	x	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15	x	Strategies for achieving adequate participant enrolment to reach target sample size
			Methods: Assignment of interventions (for controlled trials)
Allocation:			

Sequence generation	16a	x	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
Allocation concealment mechanism	16b	x	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	x	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a	x	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	x	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
			Methods: Data collection, management, and analysis
Data collection methods	18a	x	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b	x	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	x	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a	x	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b	x	Methods for any additional analyses (eg, subgroup and adjusted analyses)

	20c	x	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
			Methods: Monitoring
Data monitoring	21a	x	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
	21b	x	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22	x	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23	x	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
			Ethics and dissemination
Research ethics approval	24	x	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	25	x	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a	x	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	x	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	x	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	28	x	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29	x	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators

Ancillary and post-trial care	30	x	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	x	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	x	Authorship eligibility guidelines and any intended use of professional writers
	31c	x	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices			
Informed consent materials	32		Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33		Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Protocol for The Impact of CBT for Insomnia on Pain Symptoms and Central Sensitization in Fibromyalgia: A Randomized Controlled Trial

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Protocol for The Impact of CBT for Insomnia on Pain Symptoms and Central Sensitization in Fibromyalgia: A Randomized Controlled Trial

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ABSTRACT

Introduction: Approximately 50% of individuals with fibromyalgia (a chronic widespread pain condition) have comorbid insomnia. Treatment for these comorbid cases typically target pain, but growing research supports direct interventions for insomnia (e.g., Cognitive Behavioral Treatment for Insomnia, CBT-I) in these patients. Previous research suggests sustained hyperarousal mediated by a neural central sensitization mechanism may underlie insomnia and chronic pain symptoms in fibromyalgia. We hypothesize CBT-I will improve insomnia symptoms, improve clinical pain and reduce central sensitization. The trial will be the first to evaluate the short and long-term neural mechanisms underlying insomnia and pain improvements in fibromyalgia. Knowledge obtained from this trial might allow us to develop new or modify current treatments to better target pain mechanisms, perhaps reversing chronic pain or preventing it.

Methods & Analysis: Female participants (N=130) 18 years of age and older with comorbid fibromyalgia (with pain severity of at least 50/100) and insomnia will be recruited from the University of Missouri in Columbia, MO, and surrounding areas. Participants will be randomized to 8 weeks (plus 4 bimonthly booster sessions) of CBT-I or a Sleep Hygiene control group (SH). Participants will be assessed at baseline, post-treatment, 6 and 12-month follow-ups. The following assessments will be completed: 2 weeks of daily diaries measuring sleep and pain, daily actigraphy, insomnia severity index, pain-related disability, single night of polysomnography recording, arousal (heart rate variability, cognitive affective arousal), structural and functional magnetic resonance imaging to examine pain-related neural activity and plasticity, and mood (depression, anxiety).

Ethics & Dissemination: Ethics approval was obtained in July 2018 from the University of Missouri. All data is expected to be collected by 2022. Full trial results are planned to be published by 2024. Secondary analyses of baseline data will be subsequently published.

Clinical Trial Registration Number: NCT03744156

STRENGTHS AND LIMITATIONS OF THIS STUDY

- 8-week Cognitive Behavioral Therapy for Insomnia integrates sleep education, hygiene, stimulus control, sleep restriction, relaxation, and cognitive restructuring techniques and will be examined relative to an active sleep hygiene (SH) control in patients with comorbid fibromyalgia and insomnia.
- Pain severity cutoff criteria maximizes potential to observe clinical and neural pain-related improvements following CBT-I.
- Investigation of neural pain mechanisms underlying effects of CBT-I relative to an active control will further understanding of central mechanisms underlying sustained pain in fibromyalgia.
- 6 and 12-month follow-up will enable examination of persistence of behavioral and neural outcomes of CBT-I.
- Potential limitations include participant attrition at follow-up, which may contribute to selection bias associated with systematic differences between participants completing CBT-I versus SH. Additionally, there is no healthy control comparison group, thereby we will be unable to determine whether neural mechanisms of chronic pain are specific to fibromyalgia patients or generalizable to the broader population.

INTRODUCTION

Background

Chronic pain imposes a substantial public health burden, afflicting over 100 million Americans, with annual costs estimated at over $500 billion.[1] Individuals with chronic pain consume more health care services, yet 40% report inadequate management of their pain.[2] Chronic insomnia (at least 3 months of difficulty initiating and/or maintaining sleep orearly morning awakening, accompanied by dysfunction in at least one area of daytime functioning such as social, occupational, educational, academic, behavioral, etc.)[3] is highly comorbid with pain, affecting at least 50% of chronic pain patients.[4] Recent research suggests chronic insomnia can lead to the development or worsening of chronic pain.[5] Thus, research efforts to prevent, and treat chronic pain should consider sleep disturbance as a primary intervention target.[5]

The relationship between fibromyalgia (a chronic condition characterized by widespread pain) and sleep disturbance is well established (e.g., see Harding's 1998 review[6]). Research on fibromyalgia has linked reports of restful sleep with less reported discomfort and fatigue,[7] and nonrestorative sleep with exacerbation of pain.[8] Polysomnographic studies have identified sleep architecture differences in fibromyalgia patients versus healthy controls (i.e., increased sleep onset latency,[9] lighter sleep,[9 10] more arousals,[11-13] reduced deep sleep[9 11 12]). More than 50% of persons with fibromyalgia meet insomnia criteria,[14 15] and fibromyalgia diagnostic criteria were recently revised to include sleep disturbance as a core feature.[16] The causal role of sleep in the etiology of chronic pain has gained empirical support.[17 18] Longitudinal, experimental, and trial evidence over the past decade suggest sleep may be a more reliable predictor of chronic pain, than vice versa.[5 19] When chronic pain and insomnia co-occur, treatment typically focuses on pain. The insomnia is considered a symptom and thus, is expected to improve following improvement in pain. However,

a growing body of research,[5] including our recent trial,[20] supports direct intervention for insomnia in the context of pain.

Fibromyalgia is characterized by chronic widespread pain, central sensitization (CS) and mechanical allodynia.[15] The predominant pathophysiology of pain in FM is abnormal central pain processing or CS.[15] CS is characterized by increased responsiveness of the central nervous system (CNS) to noxious and non-noxious stimuli. Hyperalgesia and allodynia, important consequences of CS, are related to increased excitability of spinal and supraspinal neurons.[21] Patients with fibromyalgia have a higher rate of temporal summation of heat-evoked second pain (TSSP), a proxy for CS, compared to pain-free controls.[21] TSSP (aka wind-up) and subsequent aftersensations are greatly prolonged in FM.[21] Importantly, mechanical allodynia, enhanced wind-up, and prolonged aftersensations represent CS features found to be relevant predictors of fibromyalgia clinical pain.[22]

The Cognitive Activation Theory of Stress (CATS) posits chronic arousal leads to changes in the CNS consistent with CS.[23] CATS provides a framework illustrating the mechanisms by which CBT-I can improve pain. CATS proposes that through chronic arousal and insomnia (which has been linked to arousal – as described below), there are critical changes to hypothalamic-pituitary-adrenal (HPA) and CNS functioning that prompt increased sensitivity to stimulation, particularly pain.[23] We propose CBT-I improves pain by reducing arousal and improving sleep; thereby, reversing the negative HPA and CNS changes (i.e., reversing CS) that sustain chronic pain. Cognitive factors are key contributors to arousal in CATS and have a strong empirical basis to support their relationship to insomnia and chronic pain.[7 24] Chronic arousal and poor sleep, via their effects on the nervous system, are plausible candidates for explaining the relationships of

cognitive states (catastrophizing, somatic focus) and ongoing nociceptive input[8] to CS and chronic pain.

Hyperarousal is a well-established maintenance factor of chronic insomnia.[25] Persons with insomnia often develop increased cognitive focus and catastrophizing cognitions (e.g., "I will never sleep well again.") that increase arousal and interfere with getting good sleep. Cognitive therapy (a component of CBT-I) effectively targets and replaces such thoughts (e.g., "Everyone sleeps poorly on occasion."); thereby, reducing cognitive arousal and improving sleep. Previously, we found CBT-I produced large, significant improvements in sleep- and pain-related cognitive-affective arousal.[20] However, because arousal is a multidimensional construct, we have included multiple measures in the present trial – cognitive [non-specific (perceived stress), condition specific (dysfunctional sleep cognitions, pain catastrophizing)] and peripheral (heart rate variability, HRV). In terms of peripheral arousal, studies have found alterations in heart rate (HR) and heart rate variability (HRV) while awake before sleep and during Stage-2 non-REM sleep,[26] increased low frequency power and decreased high frequency power across all sleep stages,[27] and lower wake-to-sleep heart rate reduction and standard deviation of RR intervals (SDNN),[28] in persons with chronic insomnia compared to controls, consistent with increased sympathetic activity. An uncontrolled study in patients with primary insomnia found alterations of HRV following CBT-I.[29] Given our theoretical framework that CBT-I will prompt a reduction of arousal, we expect a decrease of sympathetic activity (i.e., increase in HRV) at post-treatment and both follow-ups in the proposed study.

Pain is multidimensional and evidence indicates different brain regions,[30] CNS pathways,[31] and functional interactions[32] are dynamically involved in creating the subjective pain experience. Research has identified changes in neural activity in a variety of brain regions that are positively

correlated with pain.[33 34] These regions comprise various neural networks involved with processing different dimensions of the pain experience: parts of medial and posterior thalamus, somatosensory cortices (S1/S2), insular cortical areas (posterior, mid, anterior insula), cingulate cortical areas (subgenual and pregenual anterior cingulate, anterior midcingulate, posterior cingulate), caudate/putamen, and cerebellar areas.[35-37] The purpose of neuroimaging in the current trial is to increase knowledge of the underlying neural mechanisms associated with chronic pain and how to manipulate them to treat chronic pain by targeting insomnia. Consistent with CATS,[38] our fMRI results suggest chronic pain may result from abnormal pain modulation processes. In our previous imaging work, results indicated aberrant pain processing seen in fibromyalgia is due to sustained arousal across common pain processing networks.[39 40] Moreover, we identified treatment related changes in neural activity among brain regions involved in the cognitive and affective dimensions of pain.[32 41]

Fibromyalgia is associated with gray matter atrophy in the amygdala, cingulate, insula, medial frontal cortex, parahippocampus, and prefrontal cortex.[18 42-44] Neuroimaging research has also associated chronic insomnia with reduced gray matter in the amygdala, orbitofrontal cortex, and precuneus.[45 46] Of particular interest, several studies have examined the Default Mode Network (DMN) and found both fibromyalgia[47 48] and insomnia[49 50] are characterized by heightened activity and connectivity patterns not typically observed in healthy persons. The present trial will be the first to examine CBT-I's impact on the DMN in patients with fibromyalgia and comorbid insomnia.

The efficacy of CBT-I is well established. The vast majority (~70-80%) of persons with insomnia treated behaviorally show sleep improvements that maintain through follow-ups up to 2 years, and patients rate behavioral techniques as more acceptable than sleep medications.[17] Unlike

sleep medications, behavioral approaches do not pose serious side effects and may be more cost effective in the long-run.[51] A meta-analysis[52] of non-pharmacological interventions for insomnia (all involved at least one component of CBT-I) in chronic pain patients (11 RCTs, 3 involving fibromyalgia) found large sleep quality improvements and small to moderate pain reductions following treatment. Sleep quality effects were maintained at 1 year. To date, most CBT-I trials in chronic pain patients,[52] and the two CBT-I trials in fibromyalgia[53 54] have not required a specific minimum level of pain severity for inclusion. Thus, it is possible that individuals with low levels of pain were included in these trials and did not have high enough initial pain severity to show substantial improvement.

The proposed trial examines the novel hypothesis that sustained improvements in arousal, sleep, and CS will result in sustained (or possibly enhanced) pain improvements over time. Currently, the long-term effects of CBT-I on clinical pain and its underlying neural mechanisms in FM are unknown. The proposed trial offers the following methodological improvements: 1) recruitment of participants with more severe baseline pain, 2) expanded arousal outcomes (peripheral arousal, global cognitive arousal/stress, sleep- and pain-related cognitive-affective factors), 3) imaging follow-ups at 6 and 12 months, 4) booster sessions (to ensure long-term maintenance of treatment effects), 5) a credible active control–sleep hygiene (to control for attentional/nonspecific therapeutic effects), and 6) inclusion of moderation/mediation analyses. The proposed trial addresses key shortcomings in our current understanding of chronic pain.

Aims

The overarching goal of this randomized controlled trial is to study effects of CBT-I on objective and subjective measures of sleep, arousal, and pain, as well as examine the temporal relationships between our hypothesized mediators (sleep and arousal) and pain. In our recent trial,

CBT-I prompted larger initial improvements in sleep[20] and CS[55] than did Cognitive Behavioral Treatment for Pain (CBT-P). Given sleep and CS's hypothesized mediating roles, we focus on CBT-I only here as the intervention. Additionally, given potential impact of non-specific therapeutic factors on outcomes, we compare CBT-I to an active and credible control condition, SH.

Our first specific aim is to examine the effects of eight weeks of CBT-I relative to eight weeks of sleep hygiene control (SH) on arousal (heart rate variability, cognitive-affective-dysfunctional sleep and pain cognitions, perceived global stress), subjective/objective sleep (sleep onset latency, wake after sleep onset, sleep efficiency and quality; insomnia impact), pain after treatment and at 6 and 12 month follow-ups. Our second specific aim is to examine CBT-I's effect on resting state brain activity as well as neural activation patterns of functional brain networks and Blood-Oxygen-Level Dependent (BOLD) responses to painful stimuli in regions associated with pain processing. Our third specific aim is to study CBT-I's long-term effect on structural characteristics of pain-related brain regions. Finally, our fourth aim is to examine the mediating impact of arousal, sleep, and CS on pain.

METHODS

Trial Design and Study Setting

Female patients (18 years of age and older) with fibromyalgia and chronic insomnia will be recruited from the University of Missouri in Columbia, MO, and surrounding area. Participants will be recruited through physician referral from Rheumatology, Internal Medicine and Sleep Clinics as well as community advertisements. Participants will be randomized to 8 weeks of CBT-I or sleep hygiene (SH). Both groups will receive 4 bimonthly phone booster sessions (B; See Figure 1). Baseline, post-treatment, and 6 and 12 month follow-ups will measure sleep, arousal, neural

plasticity, and pain. All participants will sign written informed consent. Participants will be compensated $150 following the baseline, post-treatment, 6 and 12 month follow-up assessments. All procedures were approved by the University of Missouri Institutional Review Board on July 11th 2018.

Eligibility Criteria

Inclusion criteria are: 1) female, 2) 18+ years of age, 3) willing to be randomized, 4) can read and understand English, 5) diagnosed with fibromyalgia [a) pain for 6+ months that is b) confirmed by tender point test (with application of 4kg force, participant reports pain in at least 11 of 18 points, including points in all four body quadrants,[15] and c) baseline diaries indicate average pain intensity of ≥50/100] and insomnia [a) insomnia complaints for 6+ months that b) occur despite adequate opportunity and circumstances for sleep, and c) consist of 1 or more of the following: difficulty falling asleep, staying asleep, or waking up too early, d) daytime dysfunction (mood, cognitive, social, occupational) due to insomnia, e) baseline diaries indicate >30 minutes of sleep onset latency or wake after sleep onset on 6 or more nights], 6) no prescribed or over the counter pain or sleep medications for 1+ month, or stabilized on medications for 6+ weeks.

Exclusion criteria are: 1) unable to provide informed consent, 2) cognitive impairment (Mini-Mental State Examination <26), 3) sleep disorder other than insomnia [i.e., sleep apnea (apnea/hypopnea index, AHI >15), Periodic Limb Movement Disorder (myoclonus arousals per hour >15)], 4) bipolar or seizure disorder (due to risk of sleep restriction treatment), 5) other major psychopathology except depression or anxiety (e.g., suicidal ideation/intent, psychotic disorders), 6) severe untreated psychiatric comorbidity (e.g., schizophrenia, substance use disorder), 7) psychotropic or other medications (e.g., beta-blockers) that alter pain or sleep, 8) participation in

non-pharmacological treatment (including CBT) for pain, sleep or mood outside current trial, 9) internal metal objects or electrical devices, 10) pregnancy.

Randomization

Biostatistician (C.D.) will select block size and perform randomization. Other personnel (except for therapists and project coordinator) will be blinded to randomization. Blocking guarantees balance, increases power,[56] and will be accounted for in analyses.

Procedures

Screening

Screening to assess fibromyalgia and insomnia symptoms and to rule out sleep disorders other than insomnia is carried out in four stages:

Stage 1: Brief Screener (~10 mins). The project coordinator will conduct a brief structured interview to address inclusion/exclusion criteria and establish probable FM and insomnia diagnoses.

Stage 2: Clinical Interview (~50 mins). The assessor will: 1) conduct a semi-structured pain, sleep, and psychiatric in-person interview, 2) perform tender point testing. Diagnosis of fibromyalgia will be overseen by a rheumatologist (C.S.).

Stage 3: Polysomnography (PSG; 1 overnight). One night of polysomnography will rule out sleep disorders other than insomnia (i.e., apnea, PLMD). The assessor will prepare participants for PSG in their own homes, and participants will sleep in their own beds. Referrals will be made for those disqualified to a neurologist (P.S.).

Stage 4: Sleep Diary Confirmation of Insomnia (~5 mins/day). Baseline sleep diaries will be used to confirm insomnia diagnosis and must show: >30 minutes of sleep onset latency or wake after

sleep onset on 6+ nights during the 2 weeks. Sleep diaries will be collected electronically via an online data management system (Qualtrics) with personal web-enabled devices or (if needed) study provided devices. Diagnosis of insomnia will be overseen by a sleep psychologist (C.S.M.).

Interventions

Both interventions include 8 weekly, 50 minute individual face to face sessions with a therapist (predoctoral graduate students in an APA accredited clinical or school psychology program at the University of Missouri) and 4 bimonthly, 20 minute phone booster sessions. SH will meet on the same schedule as CBT-I, controlling for therapist attention and other nonspecific therapeutic factors. Session content for CBT-I and SH are provided in Tables 1 and 2, respectively.

Treatment Integrity

Lichstein's[57] 3-step method will be used to measure Treatment Integrity.

1. Treatment Delivery/Training

Therapists will use manuals. Practice will begin with mock sessions and then recorded sessions with volunteers. The Principal Investigator (PI; C.S.M.) will score all training sessions. Training will last ~16 weeks until therapists obtain mastery (scoring 100 on each session's Treatment Delivery Score Sheet). For assessment of participant treatment delivery, all sessions will be recorded. Fifty percent will be scored by consultant (registered psychologist). Senior consultant (registered psychologist) will double score initial 10 treatment and 10 booster sessions to establish fidelity, and 10% of remaining sessions for reliability. Consultants will inform the PI of scores <95% for supervisory/training purposes. The PI will review 25% and therapists will review 25% of each other's sessions for ongoing training/supervision. Only consultant reviews will be used to assess fidelity.

2. Treatment Receipt

To ensure treatment comprehension, participants will be encouraged to ask questions. Workbooks describe and reinforce treatment content. To assess treatment receipt, participants will complete a brief quiz at end of Session 4.

3. Treatment Enactment

To ensure home assignments are done, workbooks contain written instructions on home assignments. To assess enactment, participants will maintain daily electronic diaries and logs.

Treatment Credibility and Expectancy

At the end of Session 3, participants will complete a treatment credibility questionnaire. This 4-item scale assesses the participant reaction to therapist and treatment efficacy, and participants provide ratings of 1 (strongly disagree) to 10 (strongly agree). Higher scores represent better treatment credibility. At the end of session 3 therapists will complete an expectancy for improvement scale.

Outcomes

A summary and timeline of study outcomes are provided in Tables 3 and 4.

Study Timeline

The study timeline is provided in Table 5.

Analytical Approach

Power Analysis

Effect sizes in our prior trial that were small for pain (*f*=.2), medium to large for sleep (*f*=.31-39), large for imaging (*f*=.69-1.13), and large for pain- and sleep-related cognitive-affective arousal (*f*=.69-1.13). To ensure adequate power with an active control, effect sizes from CBT-I trials in fibromyalgia with SH control groups were considered and ranged from small to medium for pain (*f* =.15-.25; including pain-related anxiety) and small to large for sleep outcomes (*f*=.15-

.40).[3,4] Our prior trial did not measure peripheral arousal. However, based on prior research,[7] small to medium effects (*f*=.15-.25) are expected. We determined power based on the traditional RM-ANOVA approach, as there are no established procedures for accurate power estimation for Multi-level Modeling (MLM). Using G-Power[58] for RM ANOVA within-between interaction, setting α=.05, number of groups=2, number of measurements=4, and correlations between repeated measures=.5, minimum statistical power=.8, the sample size required to detect a small effect of *f* =.15 is 62. For the mediation model tested in Aim 4, given that the ESs of the mediating paths range from small to large (*f*=.15 to .40), a sample size of 130 provides sufficient power (>.8) to detect the mediation effects on pain.[59]

Missing Values

Missing data will also be accounted for using MLM. This statistical procedure can handle missing data at all levels except the highest, which in our case, is level 2. When collecting measurements from the same people over time, some may not complete the study. Unlike RM ANOVA which would exclude these participants' data from analysis, with MLM, their information is retained in the prediction model which increases statistical power. Additional steps will be followed: 1-group dropout rates will be compared using chi-square analyses, 2-demographic and dependent variables will be examined for relationship to dropout, using related variables to impute missing values in analyses below (via SPSS Missing Items Analysis), 3-comparison of completers vs. imputated analyses to further estimate dropout effects.

Baseline demographics and participant characteristics

Group differences in baseline demographics and clinical characteristics will be analyzed using independent sample t-tests for continuous variables (age, number of health conditions, BMI, Mini Mental State Examination, duration of fibromyalgia, duration of insomnia) and chi-square

analyses for categorical variables (sex, marital status, ethnicity, employment status, education, sleep or pain medication usage). Any variables that are significantly different between groups will be entered as covariates in all analyses

Evaluations of Aims

Testing of Aim 1

To examine the effects of CBT-I on arousal, sleep, and pain in fibromyalgia patients, we will use Testing of Aim 1: To examine the effects of CBT-I on arousal, sleep, and pain in patients with fibromyalgia and insomnia, we will use a 2-level MLM. The first level will be the repeated measure over time nested within the second level which is the person-level data. Group (CBT-I, SH) will capture the between subjects variability, while time (baseline, post-treatment, 6 months, 12 months) will capture within-subject variability. Based on a priori hypotheses, separate MLMs will be conducted for each sleep, arousal, and pain outcome. Planned contrasts will be conducted consistent with a priori hypotheses. Bonferroni adjusted p-values will control family-wise error (FWE). Using a MLM approach allows us to not only compare group means like in a RM ANOVA, but also make comparisons at the individual level. Using an MLM approach, we can answer questions such as: do participants differ at specific time points on the outcome in terms of treatment, do slopes differ in terms of treatment or across participants, do specific time points vary among individuals. MLM allows for comparison of individual trajectories and comparisons between participants.

Clinical significance will also be evaluated for insomnia and pain intensity. Because there are no established clinical significance guidelines for insomnia, participants will be classified as no longer meeting trial criteria for difficulties initiating and maintaining sleep (i.e., self-reported SOL or WASO > 30 minutes on 3 or more days out of 14) at post-treatment, 6-month follow-up,

and 12-month follow-up. We will also compare responders (those who no longer meet criteria for insomnia) vs. non-responders (those who still meet criteria for insomnia) on all outcomes using independent sample t-tests. In terms of pain, participants will be classified as moderately and substantially improved (pain intensity decreases of 30%, and 50%, respectively) based on provisional benchmarks recommended for determining clinically important differences in pain intensity in clinical trials by the IMMPACT (Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials) Consensus Panel.[60] These improvement benchmarks will be examined for both morning and evening pain intensity. Group differences will analyzed using chi-square.

Testing of Aim 2

Resting State

To better understand the effects of treatment on basal brain activity, we will characterize the changes in resting state (RS) data associated with behavioral changes over time. Toward this end we will use GIFT to perform independent component analyses (ICA) of the RS data. This procedure will decompose the data into discrete components, each representing the unique time course of the brain regions associated with that component (i.e., a unique spatial-temporal map). This analytic approach will allow us to identify common (across all groups) and group specific temporal-spatial ICAs representing the DMN, its subnetworks, pain-related networks, those involved with affective processing and others (e.g. sensorimotor networks, saliency network, frontoparietal executive networks etc.). Once identified, GIFT will then be used to test for changes in the effective connectivity and functional coherence among these networks and their component brain regions. Then the influence of covariates can then be added to the analyses to examine their influence on specific nodes and overall functional coherence of the network. We will also compare

the component representative of the DMN (i.e., a specific spatial-temporal map) from each group to a study specific DMN map to calculate group specific differences. By comparing these differences to a standardized DMN template (of healthy controls that is included in GIFT), we can make statistical inferences about group related differences and treatment related changes over time.

Using the approach outlined above we anticipate that the component best representing the DMN in both groups will include most, if not all of the following Brodmann areas: BA 11 - Orbitofrontal area (orbital and rectus gyri), BA 32 - Dorsal anterior cingulate cortex, BA 9 - Dorsolateral prefrontal cortex, BA 10 - Anterior prefrontal cortex (most rostral part of superior and middle frontal gyri), BA 47 - Orbital part of inferior frontal gyrus, BAs 23 & 31 the ventral and dorsal aspects of the posterior cingulate cortex, BA 39 - Angular gyrus, BA 40 - Supramarginal gyrus, BA 37 - Fusiform gyrus, and BAs 30 & 36 of the parahippocampal gyrus. Because participants have chronic pain we expect overlapping pain-related regions to be included (e.g., BAs 40, 30, 31). However, given the tonic nature of chronic pain, we expect the DMN might also involve additional pain-related brain regions such as: BAs 4 - primary motor cortex, 6 - premotor cortex, 16 - insular cortex, and 46 - dorsolateral prefrontal cortex.

fMRI

Using a flexible analytical approach involving Multilevel Modeling (MLM) and Random Effects General Linear Models (RFX-GLMs) we will test for group differences in reported pain and associated pain-related patterns of activity and how those results vary as a function of treatment response and time. To clarify treatment related changes to painful stimuli we will identify brain regions of interest (ROIs) wherein the stimuli are significantly convolved with a hemodynamic response function (HRF). When identifying potential ROIs, a combination of criteria are used to guard against Type-I errors. These criteria are: A) p-value ≤ 0.05, using the

false discovery rate (FDR) and family wise error (FWE) corrections; B) a spatial-extent of 50+ contiguous voxels and a minimum volume of 100μL; and C) the center of mass-gravity/peak voxel in a targeted region. Because all of the imaging data will be in standardized MNI space, the coordinates of targeted regions will be checked against the standardized Wake Forest Pick Atlas. The combination of these criteria establish an image-wise p-value of 0.00002 and an effective pixel-wise alpha of $p \leq .0002$.[61] This approach will allow us to include additional criteria such as small volume corrections during analyses which may also include Area under the curve, growth curve modeling and cluster analyses may also be used to test for group related differences, over time, in HRF characteristics relative to treatment response, and the predictive ability of outcome measures. With the aforementioned analytical approach we anticipate to identify pain-related activity among typical pain-related brain regions such as: the thalamus, supplementary motor area, primary and secondary somatosensory cortices, anterior and posterior insula, dorsal anterior cingulate cortex, and the dorsolateral prefrontal cortex. We hypothesize that these, and other pain-related, regions will not only be identified at baseline, but that they will be sensitive to treatment effects and changes in other behavioral outcome measures over time.

Testing of Aim 3

Structural MRI

To study CBT-I's long-term effect on structural characteristics of pain-related brain regions, we will use the FSL tissue segmentation pipeline for analysis of cortical ribbon changes. The FreeSurfer Longitudinal Processing pipeline is highly specialized to provide unbiased results about longitudinal changes using common and within subject templates, allowing for significant increases in reliability and statistical power.[62] The pipeline accounts for inherent auto correlations in the data due to repeated sampling allowing us to assess changes among outcome measures (e.g.,

arousal, sleep, pain, and gray matter thickness, in ROIs) within/between groups at each interval and longitudinally. Based on the literature and our previous results, we anticipate finding significant changes among the somatosensory cortices, cingulate cortices (anterior, mid-dorsal), dorsolateral prefrontal cortex, frontal gyri (superior, middle, inferior), insula (anterior, posterior), temporal gyri, thalamus, and periaqueductal gray and their relationship to additional outcome variables. gray.[39 40 63-66]

Diffusion Weighted Imaging (DWI)

The diffusion weighted images will be processed via FMRIB's Diffusion Toolbox (FDT) to examine white matter characteristics diffusion weighted images. DWI measures the diffusion of water across cell membranes in 3D. Because of this, the directionality of the diffusion (anisotropy), can be determined. The FDT pipeline will estimate the apparent diffusion coefficient (ADC - amount of diffusion possible independent of direction) and fractional anisotropy (FA - an index (0 [isotropic diffusion] - 1 [diffusion along one vector]) at the individual and group levels. Higher values of FA and reduced ADC represent increased complexity of brain tissue.[67 68] Higher values of FA and reduced ADC represent increased complexity of brain tissue.[67 68] We will map white matter tracts and model connections among brain regions with probabilistic tractography.[44 69 70] As this will be a novel contribution to the field we anticipate potential changes in FA and ADC along the prefronto-subcortical dorsolateral-prefrontal and anterior cingulate-prefrontal pathways.

Testing of Aim 4

Finally, to examine the mediating impact of arousal, sleep, and CS on the effects of CBT-I on pain (Aim 4), we will use 4-wave cross-lagged path analysis. Controlling for baseline, autoregressions, and reciprocal effects among sleep, arousal (HRV, cognitive arousal, stress), and

CS (neural factors), we will examine whether CBT-I continues to predict improved sleep and decreased arousal and CS at 6 mos, and then predicts pain at 12 mos. Mediation effects of arousal, CS, and improved sleep of impact of CBT-I on pain outcomes at 12 months will be estimated. We will evaluate whether mediation effects remain significant after controlling for global and pain- and sleep-specific cognitive-affective variables.

Patient and Public Involvement

Patients and public are not involved in any of the following study procedures: development of research questions and outcome measures, study design, participant recruitment, plan for results dissemination, assessment of burden of intervention.

Ethics and Dissemination

All study procedures were approved by the Institutional Review Board at the University of Missouri on July 11th 2018. An independent 4 member Safety Monitoring Committee (SMC) was assembled in January 2019 to oversee the study. Members include those with expertise in fibromyalgia, chronic insomnia, sleep medicine and CBT. All SMC members attested that they have no conflicts of interest. The SMC met once via conference call at the beginning of the study to review the study protocol, Manual of Operating Procedures (MOOP), Informed Consent Form, and monitoring plan with emphasis on data integrity and patient safety issues. Following this initial meeting, the SMC will meet every 6 months to review progress reports prepared by the team biostatistician. Those SMC reports will include interim statistical analyses. Any changes to these procedures that are recommended by the SMC will be adopted. The SMC will review adverse events and monitor study results, focusing on efficacy, recruitment progress, randomization, compliance, retention, protocol adherence, operating procedures, forms completion, intervention effects, participant safety, and minority inclusion. The PI registered the study within

ClinicalTrials.gov (NCT03744156) on November 16th, 2018. The PI will also submit annual reports to the funding agency.

Results from this trial will be presenting at national conferences, including the Associated Professional Sleep Societies (APSS or SLEEP) and the American Pain Society, in the final year of the project. Dissemination will also occur through the submission of a primary article on the outcomes, a second article focusing on the functional neural changes (i.e., resting state and fMRI results), a third article focusing on the structural neural changes, and a fourth focusing on outcome mediation. The treatment materials will be shared electronically and will be widely available to clinicians.

Table 1. Session Content for CBT-I

Session Number	Content
1. Sleep Education	Participants will be provided with education on sleep stages; sleep and fibromyalgia; and circadian rhythms and sleep. This information is given to provide a heuristic background for the specific sleep techniques used.
2. Sleep Hygiene (SH)	SH will be discussed and participants are instructed to adhere to the following rules: 1-Avoid caffeine after noon, 2-Within 2 hours of bed, avoid exercise, nicotine, alcohol, and heavy meals, 3-Within 1 hour of bedtime, avoid screen time. The goal of SH is to eliminate sleep-interfering behaviors.
3. Stimulus Control (SC) & Brief Relaxation	SC will be discussed and participants will be asked to adhere to the following recommendations: 1-Do not use bed/bedroom for anything but sleep (or sex), 2-If not asleep in 15-20 mins, leave bed, do something non-arousing in another room. Return to bed when sleepy. If not asleep in 20 mins, repeat., 3-If awake & not back asleep in 20 mins, repeat #2, 4-Avoid napping. The goal of SC is to break incompatible/build compatible sleep associations. In addition, a 10 min relaxation exercise will be recorded and given to participants for practice at bedtime & once during the day. The goal of this is to induce relaxation/reduce arousal.
4. Sleep Restriction	A time in bed prescription (Rx) will be set at baseline average diary reported total sleep time plus 30 mins. If this value is <5 hrs, Rx will be set at 5 hrs. The therapist and participant will work together to set regular bed/wake times consistent with Rx. The goal of sleep restriction is to regulate sleep-wake cycle and reduce awake time in bed.
5. Monitoring Automatic Thoughts	Thoughts, thought patterns and emotional reactions that interfere with getting good

	sleep (i.e., “I will never sleep well again.”) will be identified and monitored.
6. Challenging/Replacing Dysfunctional Thoughts	The validity of sleep-interfering thoughts will be challenged and replaced with sleep conducive ones (i.e., “There are things I can do to improve my sleep.”)
7. Practical Recommendations	Established cognitive restructuring techniques (i.e., reappraisal, reattribution, and decatastrophizing) will be taught.
8. Review and Maintenance	Learned skills and importance of a regular sleep schedule and good sleep habits will be reviewed. Continued use of the techniques learned will be discussed.
Booster Sessions	In this brief (~20 mins) telephone session, techniques from Session 1-8 will be reviewed. The therapist will encourage continued practice of techniques. Problems will be trouble-shooted.

Table 2. Session Content for SH

Session Number	Content
1. Sleep Education	Content is the same as CBT-I
2. Sleep Hygiene (SH)	Content is the same as CBT-I.
3. Insomnia and Pain	Participants are provided education on chronic/acute insomnia (Spielman's 3 P's Model)[53] and the Gate Control Theory[54] of Pain.
4. Environment	Participants are provided with education on SH rules related to environmental factors (e.g., noise, light).
5. Lifestyle	Participants are provided with education on lifestyle factors that influence sleep (e.g., use of stimulants & other substances).
6. Diet	Participants are provided with education about diet and nutrition and their influence on sleep.
7. Exercise	Participants are provided with education about exercise and its influence on sleep.
8. Review and Maintenance	In the final session, SH training reviewed and continued practice is encouraged. Problems are trouble-shooted. All education provided in previous sessions will be reviewed. Finally, continued engagement in education will be discussed.
Booster Sessions	As in CBT-I, all training and education covered in SH training will be reviewed in a brief (~20 mins) telephone call. Continued SH practice and education engagement are encouraged. Problems are trouble-shooted.

Table 3. Outcome Measures

Outcome Category	Measure	Primary/Secondary	Details
Subjective Sleep	Daily Sleep Diaries	Primary	Online diaries will be completed each morning (~5 mins) during each 2 week assessment period and 8 weeks of treatment. Primary outcome variables include: sleep onset latency (SOL; time from initial lights-out until sleep onset), wake after sleep onset (WASO; time awake after initial sleep onset until last awakening), number of awakenings, total sleep time, sleep efficiency (total sleep time/time spent in bed × 100), and sleep quality rating (1-very poor to 7-excellent). Sleep and pain medication consumption variables will include: name, dosage, and time taken. Sleep medication will be converted to number of lowest recommended dosage (LRD) units,[71] and pain medication to morphine equivalent dosage (MED).[72]
	Insomnia Severity Index (ISI)	Primary	At each time point, participants will complete the ISI (primary outcome).[73] The ISI is a seven item questionnaire that assesses the frequency and/or severity of insomnia symptoms [e.g., "rate the current severity of your difficulty falling asleep"; choices range from 0 (none) to very severe (5)], as well as questions regarding the impact of insomnia on daytime functioning [e.g., "to what extent do you do you consider your sleep problem to interfere with your daily functioning (e.g. daytime fatigue, mood, ability to function at work/daily chores, concentration, memory, mood, etc.) currently?; choices range from 0 (not interfering at all) to 5 (very much interfering). Total scores on the ISI range from 0-28, with higher scores representing more severe insomnia.
Objective Sleep	Daily Actigraphy	Secondary	Actiwatch 2® (Philips Respironics) is a watch-like device that monitors light and gross motor activity. Data will be analyzed by proprietary software using 30s epochs. A validated algorithm estimates the same variables (secondary outcomes) provided by diaries (except sleep

			quality). Participants wear the device 24/7 during each 2 weeks of assessment, and 8 weeks of treatment.
	Polysomnographic Sleep	Secondary	The Comet-PLUS® Portable (Natus Neurology) Recording System will be used to conduct a single in-home overnight sleep study at baseline, post-treatment, and both follow-ups. Consistent with ambulatory recommendations,[74] monitoring consists of 10 EEG, 2 EOG, and 3 EMG (chin) using standard placement. It also includes respiratory inductance plethysmography (thoracic/abdominal effort), oximeter (pulse/oxygen saturation), electrocardiogram (ECG), R/L anterior tibialis EMG, oral-nasal airflow thermocouple, and nasal cannula pressure transducer. We require 4 hrs of acceptable data (i.e., scorable stage/respiratory events) and follow Sleep Heart Health Study (SHHS)[94] procedures for training, data management, and scoring. PSG provides sleep stage % (stage 1, 2, 3, Rapid Eye Movement Sleep) and absolute values for diary variables (secondary outcomes).
Arousal	Peripheral Arousal – Heart Rate Variability (HRV)	Primary	Using Holter monitors, we will obtain 5 minute electrocardiogram recordings during rest in a quiet controlled environment at each assessment. Time and spectral analysis of the short-term variability of HR will be performed using Pathfinder (Spacelabs, Seattle, WA) software to assess the neural regulation of HR. The time domain indices reflect the beat-to-beat variability with respect to time. The variables standard deviation of the N-N intervals (SDNN) and the percentage of N-N intervals that exceed 50 ms (pNN50) will be examined. The frequency domain indices reflect the underlying rhythms of the mechanisms modulating heart rate. High frequency (0.15-0.4 Hz), low frequency (0.04-0.15 Hz), and very low frequency (below 0.04 Hz) spectral bands will be examined.
	Global Cognitive Arousal-Perceived Stress Scale (PSS)[96]	Primary	The PSS (primary outcome) is a 10 item questionnaire that asks participants to appraise their stress level during the past month in response to several everyday situations (e.g., "in the last month how

			often have you been able to control irritations in your life?"). Choices range from 0 (never) to 4 (very often). Higher total scores on the PSS indicate worse perceived stress.
	Insomnia-Specific Cognitive-Affective Arousal - Dysfunctional Beliefs and Attitudes about Sleep (DBAS)	Primary	The DBAS[73] is a 30 item scale that assess the degree to which an individual agrees with statements regarding sleep (e.g., "Medication is probably the only solution to sleepiness", "I need 8 hours of sleep to feel refreshed and function well during the day"). Participants rate their belief in each statement from 0 (Strongly disagree) to 10 (strongly agree). Scores for each item are summed and higher scores on the DBAS indicate worse cognitive affective arousal related to insomnia.
	Pain-Specific Cognitive-Affective Arousal-Catastrophizing-Pain Catastrophizing Scale (PCS)[75]	Primary	The PCS is a 13-item scale that measures the degree (from 0-not at all to 4-all the time) to which participants experienced certain thoughts or feelings during past painful events. Items are scored and total scores on the PCS represent worse pain catastrophizing.
Pain	Daily Clinical Pain-Electronic Daily Diaries	Primary	On the daily electronic diaries, participants provide ratings on a 0-100 scale regarding their pain intensity (0-no pain sensation, 100-most intense pain imaginable) and pain unpleasantness (0-not at all unpleasant, 100-most unpleasant imaginable).
	Subjective Pain-McGill Pain Questionnaire (MPQ)[76 77]	Secondary	The MPQ assesses participants pain symptoms across 21 categories. For each category, participants select the best word that described their pain. Qualitative responses are coded by numerical value (e.g., 1-3 or 1-5), with higher values representing worse pain in that category. If they do not experience a specific category of pain, they do not provide a response to that category. Category scores are summed and total scores could range from 0 (no pain) to 78 (severe pain).

	Patient-Centered Outcomes Ques. (PCOQ)[78]	Secondary	The PCOQ is a 5-item questionnaire that assess on a 0-10 point scale usual levels of pain, desired levels of pain, what level of improvement in treatment outcomes they would consider successful, what level of improvement in treatment outcomes they expect after treatment, importance of improvement in treatment outcomes.
	Pain-Related Disability-Pain Disability Inventory (PDI)[79 80]	Secondary	The PDI includes 7-items rated on an 11-point scale (0 = no disability, 10 = total disability) indicating the degree to which chronic pain interferes with participant functioning in the following areas: family/home responsibilities, recreation, social activity, occupation, sexual behavior, self-care, and life-sustaining activity. The seven ratings are summed to compute a total score (0-70), with higher scores indicated worse pain disability.
Mood	State Trait Anxiety Inventory (STAI)[81]	Covariate	STAI asks respondents to rate how true 20 self-descriptive statements (e.g., I feel calm) are on a 4-point scale (1 = not at all, 4 = very much so). Typically, respondents are asked to rate statements according to how they generally feel (trait-anxiety scale) and how they feel in the current moment (state-anxiety scale). Total scores range from 20 to 80, with higher scores indicating greater maladjustment.
	Beck Depression Inventory – 2nd Edition (BDI-II)[82]	Covariate	The BDI-II contains 21 items that measure the severity of depressive symptomatology on a three-point scale (0 = absence of symptoms, 3 = most severe). Typically, respondents answer for the previous week, but the previous two weeks were used in this study to match the two-week activity recording period for each assessment. Total scores range from 0 to 63. Ranges for clinical levels of depression are 0 to 13 (minimal), 14 to 19 (mild), 20 to 28 (moderate), and 29 to 63 (severe).
	Pain Anxiety Symptoms Scale (PASS-20)[83]	Covariate	The PASS measures fear and anxiety responses related to pain. The PASS-20 revised short form version contains 20 items in which participants must rate the frequency in which they experience fearful and anxiety ridden responses related to pain or pain-related situations.

			This scale is widely used in clinical screening of chronic pain and pain research.
	Anxiety and Preoccupation about Sleep Questionnaire (PSQ)[84]	Covariate	The APSQ measures the intensity of both daytime and nighttime worry related to insomnia. Participants are presented with 10 statements describing several sleep related worries and participants are asked to indicate how true they on a scale from 1 (not true) to 10 (very true). Scores on this scale are associated with self-reported (e.g., diary) sleep measures as well as daytime impairment, with higher scores representing worse anxiety related to sleep.
Neuroimaging	Neural Plasticity and Central Sensitization	Primary	Three imaging protocols, 1) structural MRI (MPRAGE), 2) functional MRI (EPI BOLD), and 3) Diffusion Weighted Imaging (DWI), will assess neural plasticity and central sensitization. Image acquisition Imaging data will be acquired with Siemens' new MAGNETOM Vida 3T and a 20-channel head-neck coil. The parameters for the 3D-T1-weighted structural scans are: 256 axial slices (.90*.89*.89mm3; TR=.75s, TE=0.0045s, flip angle=75°, matrix=256*256, FOV = 256mm. T2 gradient EPI sequence for the resting state and fMRI scans will use the following parameters: whole brain, 36-contiguous slices (axial), 3mm3 isotropic voxels, oriented parallel to the AC-PC plane, TR=2.46s; TE=30ms; flip angle=90◦; 76*76 matrix, and 120 volumes. The parameters for the diffusion weighted scans are: 32 slices, 1*1*3.25mm2, TR=3.6s, TE=.064s, Flip angle = 90º, directions=6. The sequence of scan acquisition is: Localizer, gradient field map, 3D anat, resting state (x2, ~5 mins), fMRI experimental pain scans (x3, ~25 mins), DTI (~12 mins). During the resting state scans, subjects are told to relax, limit movement, and try not to fall asleep. In preparation for the experimental pain scan, participants will first undergo quantitative sensory testing (QST) calibration trials outside of

the scanner, in order to determine individual pain tolerance. A computer-controlled Medoc Pain and Sensory Evaluation System (Pathway Model ATS, Medoc Advanced Medical Systems, Durham, NC) will be used to deliver thermal stimuli. QST calibration uses a series of calibration trials (CTs), to identify their pain tolerance temperature, which will be used during their experimental pain scanning session. The CTs start at 43ºC and increase by 1ºC until their tolerance, or 51ºC is reached, whichever comes first. Subjects will sit in a chair, remove their shoes and socks and extend their feet outward. A researcher will wipe the bottom of the foot with an alcohol pad, after which a contact heat thermode will be placed on the plantar surface of the foot. Each stimulus cycle is initiated by the experimenter via key press. After each stimulus, subjects will describe the sensation (pain/not painful) and rate its pain intensity on a scale from 0–no pain to 100–worst pain imaginable. Once the ratings and inter-stimulus interval have finished the cycle will be repeated until their tolerance temperature is identified (i.e., the lowest temperature with a pain intensity rating of ≥ 65). This will be the temperature that will be used during their scanning sessions

During each 5 min. experimental pain scan, thermal stimuli will be delivered with an MR compatible, computer-controlled, CHEPS Pathway system, which is a peltier-element-based stimulator, and is capable of producing stimuli across a range of temperatures (33ºC – 51ºC). The start of each scan will begin with the thermode at ambient temperature for 30s and then 16 cycles of the following: 12s at ambient temperature, then in less than two seconds the temperature will steadily increase (ramp) until reaching their pain temperature (determined by the calibration trials), and remain at that temperature (hold) for 5-seconds, followed by a variable inter stimulus interval of 12-20 seconds. Following the 16th cycle, the scan proceeds for another 30s with the thermode at ambient temperature.

Table 4. Schedule of Outcome Measures

Assessment Period	Base	Tx	Post	Boosters	FUs
Weeks	**2**	**8**	**2**	**2**	**2**
Telephone & clinical interviews, consent, MMSE	X				
Actigraph, PSG, ISI, MPQ, PDI, RH, Wind-Up, HRV, DBAS, PSS, PCS, STAI, BDI-II, PASS-20, APSQ	X		X		X
Electronic Daily Diaries	X	X	X	X	X
Tx Integrity – Delivery & Receipt, Treatment Credibility		X			

Note. MMSE = Mini Mental State Examination; PSG = Polysomnography; ISI = Insomnia Severity Index; MPQ = McGill Pain Questionnaire; PDI = Pain Disability Inventory; RH = Ramp and Hold; HRV = Heart Rate Variability; DBAS = Dysfunctional Beliefs about Sleep Scale; PSS = Pain Severity Scale; PCS = Pain Catastrophizing Scale ; STAI = State Trait Anxiety Inventory; BDI-II = Beck Depression Inventory – 2nd Edition; PASS-20 = Pain Anxiety Symptoms Scale; APSQ = Anxiety and Preoccupation about Sleep Questionnaire

Table 5. Study Timeline

Project Year→	1		2		3		4		5	
Half →	1	2	1	2	1	2	1	2	1	2
1. Develop Manual of Operating Procedures. Register with clinicaltrials.gov. Publish trial protocol. Develop SH. Train therapists & assessor.	■									
2. Recruit, collect baseline, deliver treatment		■	■	■	■	■	■			
3. Collect post-treatment assessment				■	■	■	■	■		
4. Collect 6 & 12 month follow-up assessments			■	■	■	■	■	■		
5. Offer/provide CBT-I to SH controls									■	
6. Final data analysis & dissemination (continues after grant ends); final report									■	■

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Contributors

All authors made substantial contributions to the concept and design of the study. CSM drafted initial protocol, with input from all authors. JCG, RS, MR drafted MRI protocol. CBD drafted statistical analysis plan. CSM, PS and CS drafted screening procedures. CSM and AFC drafted the manuscript. All authors revised the manuscript.

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Disclaimer

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Competing Interests

None declared.

Ethics approval

The study and methods were evaluated and approved by the Institutional Review Board at the University of Missouri (IRB Project Number: 2011835).

Provenance and peer review

Externally peer reviewed at the NINR at the NIH.

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List of Figures

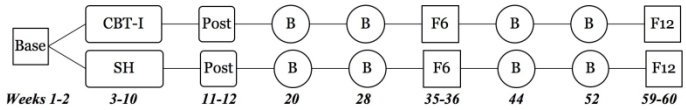

Figure 1. Timeline of Randomized Controlled Trial

215x279mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Check (x)	Description
			Administrative information
Title	1	x	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a	x	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	x	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	x	Date and version identifier
Funding	4	x	Sources and types of financial, material, and other support
Roles and responsibilities	5a	x	Names, affiliations, and roles of protocol contributors
	5b	x	Name and contact information for the trial sponsor
	5c	x	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	x	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction			
Background and rationale	6a	x	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	x	Explanation for choice of comparators
Objectives	7	x	Specific objectives or hypotheses

Trial design	8	x	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
			Methods: Participants, interventions, and outcomes
Study setting	9	x	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	10	x	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11a	x	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	x	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	x	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	x	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12	x	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	13	x	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14	x	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15	x	Strategies for achieving adequate participant enrolment to reach target sample size
			Methods: Assignment of interventions (for controlled trials)
Allocation:			

Sequence generation	16a	x	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
Allocation concealment mechanism	16b	x	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	x	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a	x	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	x	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
			Methods: Data collection, management, and analysis
Data collection methods	18a	x	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b	x	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	x	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a	x	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b	x	Methods for any additional analyses (eg, subgroup and adjusted analyses)

	20c	x	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
			Methods: Monitoring
Data monitoring	21a	x	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
	21b	x	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22	x	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23	x	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
			Ethics and dissemination
Research ethics approval	24	x	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	25	x	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a	x	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	x	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	x	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	28	x	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29	x	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators

Ancillary and post-trial care	30	x	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	x	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	x	Authorship eligibility guidelines and any intended use of professional writers
	31c	x	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices			
Informed consent materials	32		Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33		Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Protocol for The Impact of CBT for Insomnia on Pain Symptoms and Central Sensitization in Fibromyalgia: A Randomized Controlled Trial

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Protocol for The Impact of CBT for Insomnia on Pain Symptoms and Central Sensitization in Fibromyalgia: A Randomized Controlled Trial

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ABSTRACT

Introduction: Approximately 50% of individuals with fibromyalgia (a chronic widespread pain condition) have comorbid insomnia. Treatment for these comorbid cases typically target pain, but growing research supports direct interventions for insomnia (e.g., Cognitive Behavioral Treatment for Insomnia, CBT-I) in these patients. Previous research suggests sustained hyperarousal mediated by a neural central sensitization mechanism may underlie insomnia and chronic pain symptoms in fibromyalgia. We hypothesize CBT-I will improve insomnia symptoms, improve clinical pain and reduce central sensitization. The trial will be the first to evaluate the short and long-term neural mechanisms underlying insomnia and pain improvements in fibromyalgia. Knowledge obtained from this trial might allow us to develop new or modify current treatments to better target pain mechanisms, perhaps reversing chronic pain or preventing it.

Methods & Analysis: Female participants (N=130) 18 years of age and older with comorbid fibromyalgia (with pain severity of at least 50/100) and insomnia will be recruited from the University of Missouri in Columbia, MO, and surrounding areas. Participants will be randomized to 8 weeks (plus 4 bimonthly booster sessions) of CBT-I or a Sleep Hygiene control group (SH). Participants will be assessed at baseline, post-treatment, 6 and 12-month follow-ups. The following assessments will be completed: 2 weeks of daily diaries measuring sleep and pain, daily actigraphy, insomnia severity index, pain-related disability, single night of polysomnography recording, arousal (heart rate variability, cognitive affective arousal), structural and functional magnetic resonance imaging to examine pain-related neural activity and plasticity, and mood (depression, anxiety).

Ethics & Dissemination: Ethics approval was obtained in July 2018 from the University of Missouri. All data is expected to be collected by 2022. Full trial results are planned to be published by 2024. Secondary analyses of baseline data will be subsequently published.

Clinical Trial Registration Number: NCT03744156

STRENGTHS AND LIMITATIONS OF THIS STUDY

- 8-week Cognitive Behavioral Therapy for Insomnia integrates sleep education, hygiene, stimulus control, sleep restriction, relaxation, and cognitive restructuring techniques and will be examined relative to an active sleep hygiene (SH) control in patients with comorbid fibromyalgia and insomnia.
- Pain severity cutoff criteria maximizes potential to observe clinical and neural pain-related improvements following CBT-I.
- Investigation of neural pain mechanisms underlying effects of CBT-I relative to an active control will further understanding of central mechanisms underlying change in pain or insomnia in fibromyalgia, which may inform mechanisms underlying sustained pain in fibromyalgia.
- 6 and 12-month follow-up will enable examination of persistence of behavioral and neural outcomes of CBT-I.
- Potential limitations include participant attrition at follow-up, which may contribute to selection bias associated with systematic differences between participants completing CBT-I versus SH. Additionally, there is no healthy control comparison group, thereby we will be unable to determine whether neural mechanisms of chronic pain are specific to fibromyalgia patients or generalizable to the broader population.

INTRODUCTION

Background

Chronic pain imposes a substantial public health burden, afflicting over 100 million Americans, with annual costs estimated at over $500 billion.[1] Individuals with chronic pain consume more health care services, yet 40% report inadequate management of their pain.[2] Chronic insomnia (at least 3 months of difficulty initiating and/or maintaining sleep or early morning awakening, accompanied by dysfunction in at least one area of daytime functioning such as social, occupational, educational, academic, behavioral, etc.)[3] is highly comorbid with pain, affecting at least 50% of chronic pain patients.[4] Recent research suggests chronic insomnia can lead to the development or worsening of chronic pain.[5] Thus, research efforts to prevent, and treat chronic pain should consider sleep disturbance as a primary intervention target.[5]

The relationship between fibromyalgia (a chronic condition characterized by widespread pain) and sleep disturbance is well established (e.g., see Harding's 1998 review[6]). Research on fibromyalgia has linked reports of restful sleep with less reported discomfort and fatigue,[7] and nonrestorative sleep with exacerbation of pain.[8] Polysomnographic studies have identified sleep architecture differences in fibromyalgia patients versus healthy controls (i.e., increased sleep onset latency,[9] lighter sleep,[9 10] more arousals,[11-13] reduced deep sleep[9 11 12]). More than 50% of persons with fibromyalgia meet insomnia criteria,[14 15] and fibromyalgia diagnostic criteria were recently revised to include sleep disturbance as a core feature.[16] The causal role of sleep in the etiology of chronic pain has gained empirical support.[17 18] Longitudinal, experimental, and trial evidence over the past decade suggest sleep may be a more reliable predictor of chronic pain, than vice versa.[5 19] When chronic pain and insomnia co-occur, treatment typically focuses on pain. The insomnia is

considered a symptom and thus, is expected to improve following improvement in pain. However, a growing body of research,[5] including our recent trial,[20] supports direct intervention for insomnia in the context of pain.

Fibromyalgia is characterized by chronic widespread pain, central sensitization (CS) and mechanical allodynia.[15] The predominant pathophysiology of pain in FM is abnormal central pain processing or CS.[15] CS is characterized by increased responsiveness of the central nervous system (CNS) to noxious and non-noxious stimuli. Hyperalgesia and allodynia, important consequences of CS, are related to increased excitability of spinal and supraspinal neurons.[21] Patients with fibromyalgia have a higher rate of temporal summation of heat-evoked second pain (TSSP), a proxy for CS, compared to pain-free controls.[21] TSSP (aka wind-up) and subsequent aftersensations are greatly prolonged in FM.[21] Importantly, mechanical allodynia, enhanced wind-up, and prolonged aftersensations represent CS features found to be relevant predictors of fibromyalgia clinical pain.[22]

The Cognitive Activation Theory of Stress (CATS) posits chronic arousal leads to changes in the CNS consistent with CS.[23] CATS provides a framework illustrating the mechanisms by which CBT-I can improve pain. CATS proposes that through chronic arousal and insomnia (which has been linked to arousal – as described below), there are critical changes to hypothalamic-pituitary-adrenal (HPA) and CNS functioning that prompt increased sensitivity to stimulation, particularly pain.[23] We propose CBT-I improves pain by reducing arousal and improving sleep; thereby, reversing the negative HPA and CNS changes (i.e., reversing CS) that sustain chronic pain. Cognitive factors are key contributors to arousal in CATS and have a strong empirical basis to support their relationship to insomnia and chronic pain.[7 24] Chronic arousal and poor sleep, via their effects on the nervous system, are plausible candidates for explaining the relationships of

cognitive states (catastrophizing, somatic focus) and ongoing nociceptive input[8] to CS and chronic pain.

Hyperarousal is a well-established maintenance factor of chronic insomnia.[25] Persons with insomnia often develop increased cognitive focus and catastrophizing cognitions (e.g., "I will never sleep well again.") that increase arousal and interfere with getting good sleep. Cognitive therapy (a component of CBT-I) effectively targets and replaces such thoughts (e.g., "Everyone sleeps poorly on occasion."); thereby, reducing cognitive arousal and improving sleep. Previously, we found CBT-I produced large, significant improvements in sleep- and pain-related cognitive-affective arousal.[20] However, because arousal is a multidimensional construct, we have included multiple measures in the present trial – cognitive [non-specific (perceived stress), condition specific (dysfunctional sleep cognitions, pain catastrophizing)] and peripheral (heart rate variability, HRV). In terms of peripheral arousal, studies have found alterations in heart rate (HR) and heart rate variability (HRV) while awake before sleep and during Stage-2 non-REM sleep,[26] increased low frequency power and decreased high frequency power across all sleep stages,[27] and lower wake-to-sleep heart rate reduction and standard deviation of RR intervals (SDNN),[28] in persons with chronic insomnia compared to controls, consistent with increased sympathetic activity. An uncontrolled study in patients with primary insomnia found alterations of HRV following CBT-I.[29] Given our theoretical framework that CBT-I will prompt a reduction of arousal, we expect a decrease of sympathetic activity (i.e., increase in HRV) at post-treatment and both follow-ups in the proposed study.

Pain is multidimensional and evidence indicates different brain regions,[30] CNS pathways,[31] and functional interactions[32] are dynamically involved in creating the subjective pain experience. Research has identified changes in neural activity in a variety of brain regions that are positively

correlated with pain.[33 34] These regions comprise various neural networks involved with processing different dimensions of the pain experience: parts of medial and posterior thalamus, somatosensory cortices (S1/S2), insular cortical areas (posterior, mid, anterior insula), cingulate cortical areas (subgenual and pregenual anterior cingulate, anterior midcingulate, posterior cingulate), caudate/putamen, and cerebellar areas.[35-37] The purpose of neuroimaging in the current trial is to increase knowledge of the underlying neural mechanisms associated with chronic pain and how to manipulate them to treat chronic pain by targeting insomnia. Consistent with CATS,[38] our fMRI results suggest chronic pain may result from abnormal pain modulation processes. In our previous imaging work, results indicated aberrant pain processing seen in fibromyalgia is due to sustained arousal across common pain processing networks.[39 40] Moreover, we identified treatment related changes in neural activity among brain regions involved in the cognitive and affective dimensions of pain.[32 41]

Fibromyalgia is associated with gray matter atrophy in the amygdala, cingulate, insula, medial frontal cortex, parahippocampus, and prefrontal cortex.[18 42-44] Neuroimaging research has also associated chronic insomnia with reduced gray matter in the amygdala, orbitofrontal cortex, and precuneus.[45 46] Of particular interest, several studies have examined the Default Mode Network (DMN) and found both fibromyalgia[47 48] and insomnia[49 50] are characterized by heightened activity and connectivity patterns not typically observed in healthy persons. The present trial will be the first to examine CBT-I's impact on the DMN in patients with fibromyalgia and comorbid insomnia.

The efficacy of CBT-I is well established. The vast majority (~70-80%) of persons with insomnia treated behaviorally show sleep improvements that maintain through follow-ups up to 2 years, and patients rate behavioral techniques as more acceptable than sleep medications.[17] Unlike

sleep medications, behavioral approaches do not pose serious side effects and may be more cost effective in the long-run.[51] A meta-analysis[52] of non-pharmacological interventions for insomnia (all involved at least one component of CBT-I) in chronic pain patients (11 RCTs, 3 involving fibromyalgia) found large sleep quality improvements and small to moderate pain reductions following treatment. Sleep quality effects were maintained at 1 year. To date, most CBT-I trials in chronic pain patients,[52] and the two CBT-I trials in fibromyalgia[53 54] have not required a specific minimum level of pain severity for inclusion. Thus, it is possible that individuals with low levels of pain were included in these trials and did not have high enough initial pain severity to show substantial improvement.

The proposed trial examines the novel hypothesis that sustained improvements in arousal, sleep, and CS will result in sustained (or possibly enhanced) pain improvements over time. Currently, the long-term effects of CBT-I on clinical pain and its underlying neural mechanisms in FM are unknown. The proposed trial offers the following methodological improvements: 1) recruitment of participants with more severe baseline pain, 2) expanded arousal outcomes (peripheral arousal, global cognitive arousal/stress, sleep- and pain-related cognitive-affective factors), 3) imaging follow-ups at 6 and 12 months, 4) booster sessions (to ensure long-term maintenance of treatment effects), 5) a credible active control–sleep hygiene (to control for attentional/nonspecific therapeutic effects), and 6) inclusion of moderation/mediation analyses. The proposed trial addresses key shortcomings in our current understanding of chronic pain.

Aims

The overarching goal of this randomized controlled trial is to study effects of CBT-I on objective and subjective measures of sleep, arousal, and pain, as well as examine the temporal relationships between our hypothesized mediators (sleep and arousal) and pain. In our recent trial,

CBT-I prompted larger initial improvements in sleep[20] and CS[55] than did Cognitive Behavioral Treatment for Pain (CBT-P). Given sleep and CS's hypothesized mediating roles, we focus on CBT-I only here as the intervention. Additionally, given potential impact of non-specific therapeutic factors on outcomes, we compare CBT-I to an active and credible control condition, SH.

Our first specific aim is to examine the effects of eight weeks of CBT-I relative to eight weeks of sleep hygiene control (SH) on arousal (heart rate variability, cognitive-affective-dysfunctional sleep and pain cognitions, perceived global stress), subjective/objective sleep (sleep onset latency, wake after sleep onset, sleep efficiency and quality; insomnia impact), and pain after treatment and at 6 and 12 month follow-ups. We hypothesize that compared to SH, CBT-I will decrease arousal, improve sleep and decrease pain after treatment and at 6 and 12 month follow-ups. Our second specific aim is to examine CBT-I's effect on resting state brain activity as well as neural activation patterns of functional brain networks and Blood-Oxygen-Level Dependent (BOLD) responses to painful stimuli in regions associated with pain processing. We hypothesize that compared to SH, CBT-I will reduce (normalize) resting state brain activity in the DMN, which includes the cingulate cortex and medial prefrontal cortex, and reduce maladaptive pain-related brain network and BOLD activity in several regions associated with the cognitive and affective modulation of pain, including the inferior frontal gyrus, cingulate gyrus, and insula. Our third specific aim is to study CBT-I's long-term effect on structural characteristics of pain-related brain regions. We hypothesize that compared to SH, CBT-I will prompt structural changes indicative of a reversal of the maladaptive neural plasticity associated with chronic pain. Reversal will be characterized by increased gray matter volume/thickness, improved white matter integrity, and stronger structural connectivity in the lateral-orbitofrontal and anterior/rostral cingulate regions,

compared to the control following treatment and at both follow-ups. Finally, our fourth aim is to examine the mediating impact of arousal, sleep, and CS on pain. We hypothesize that CBT-I will promote pain improvements through arousal reduction, sleep improvement, and CS reversal. We hypothesize that significant improvements in all variables will be evident immediately following treatment, and that sustained improvements in arousal, sleep, and CS will mediate sustained (and possibly increased) improvements in pain at 6 and 12 months. We will also evaluate whether these mediating effects explain unique variance of pain improvement over and beyond the mediating effects of global or possibly pain- and/or sleep-specific cognitive-affective factors.

METHODS

Trial Design and Study Setting

Female patients (18 years of age and older) with fibromyalgia and chronic insomnia will be recruited from the University of Missouri in Columbia, MO, and surrounding area. Participants will be recruited through physician referral from Rheumatology, Internal Medicine and Sleep Clinics as well as community advertisements. Participants will be randomized to 8 weeks of CBT-I or sleep hygiene (SH). Both groups will receive 4 bimonthly phone booster sessions (B; See Figure 1). Baseline, post-treatment, and 6 and 12 month follow-ups will measure sleep, arousal, neural plasticity, and pain. All participants will sign written informed consent. Participants will be compensated $150 following the baseline, post-treatment, 6 and 12 month follow-up assessments. All procedures were approved by the University of Missouri Institutional Review Board on July 11th 2018.

Eligibility Criteria

Inclusion criteria are: 1) female, 2) 18+ years of age, 3) willing to be randomized, 4) can read and understand English, 5) diagnosed with fibromyalgia [a) pain for 6+ months that is b) confirmed by tender point test (with application of 4kg force, participant reports pain in at least 11 of 18 points, including points in all four body quadrants,[15] and c) baseline diaries indicate average pain intensity of ≥50/100] and insomnia [a) insomnia complaints for 6+ months that b) occur despite adequate opportunity and circumstances for sleep, and c) consist of 1 or more of the following: difficulty falling asleep, staying asleep, or waking up too early, d) daytime dysfunction (mood, cognitive, social, occupational) due to insomnia, e) baseline diaries indicate >30 minutes of sleep onset latency or wake after sleep onset on 6 or more nights], 6) no prescribed or over the counter pain or sleep medications for 1+ month, or stabilized on medications for 6+ weeks.

Exclusion criteria are: 1) unable to provide informed consent, 2) cognitive impairment (Mini-Mental State Examination <26), 3) sleep disorder other than insomnia [i.e., sleep apnea (apnea/hypopnea index, AHI >15), Periodic Limb Movement Disorder (myoclonus arousals per hour >15)], 4) bipolar or seizure disorder (due to risk of sleep restriction treatment), 5) other major psychopathology except depression or anxiety (e.g., suicidal ideation/intent, psychotic disorders), 6) severe untreated psychiatric comorbidity (e.g., schizophrenia, substance use disorder), 7) psychotropic or other medications (e.g., beta-blockers) that alter pain or sleep, 8) participation in non-pharmacological treatment (including CBT) for pain, sleep or mood outside current trial, 9) internal metal objects or electrical devices, 10) pregnancy.

Randomization

Biostatistician (C.D.) will select block size and perform randomization. Other personnel (except for therapists and project coordinator) will be blinded to randomization. Blocking guarantees balance, increases power,[56] and will be accounted for in analyses.

Procedures

Screening

Screening to assess fibromyalgia and insomnia symptoms and to rule out sleep disorders other than insomnia is carried out in four stages:

Stage 1: Brief Screener (~10 mins). The project coordinator will conduct a brief structured interview to address inclusion/exclusion criteria and establish probable FM and insomnia diagnoses.

Stage 2: Clinical Interview (~50 mins). The assessor will: 1) conduct a semi-structured pain, sleep, and psychiatric in-person interview, 2) perform tender point testing. Diagnosis of fibromyalgia will be overseen by a rheumatologist (C.S.).

Stage 3: Polysomnography (PSG; 1 overnight). One night of polysomnography will rule out sleep disorders other than insomnia (i.e., apnea, PLMD). The assessor will prepare participants for PSG in their own homes, and participants will sleep in their own beds. Referrals will be made for those disqualified to a neurologist (P.S.).

Stage 4: Sleep Diary Confirmation of Insomnia (~5 mins/day). Baseline sleep diaries will be used to confirm insomnia diagnosis and must show: >30 minutes of sleep onset latency or wake after sleep onset on 6+ nights during the 2 weeks. Sleep diaries will be collected electronically via an online data management system (Qualtrics) with personal web-enabled devices or (if needed) study provided devices. Diagnosis of insomnia will be overseen by a sleep psychologist (C.S.M.).

Interventions

Both interventions include 8 weekly, 50 minute individual face to face sessions with a therapist (predoctoral graduate students in an APA accredited clinical or school psychology program at the University of Missouri) and 4 bimonthly, 20 minute phone booster sessions. SH will meet on the same schedule as CBT-I, controlling for therapist attention and other nonspecific therapeutic factors. Session content for CBT-I and SH are provided in Tables 1 and 2, respectively.

Treatment Integrity

Lichstein's[57] 3-step method will be used to measure Treatment Integrity.

1. Treatment Delivery/Training

Therapists will use manuals. Practice will begin with mock sessions and then recorded sessions with volunteers. The Principal Investigator (PI; C.S.M.) will score all training sessions. Training will last ~16 weeks until therapists obtain mastery (scoring 100 on each session's Treatment Delivery Score Sheet). For assessment of participant treatment delivery, all sessions will be recorded. Fifty percent will be scored by consultant (registered psychologist). Senior consultant (registered psychologist) will double score initial 10 treatment and 10 booster sessions to establish fidelity, and 10% of remaining sessions for reliability. Consultants will inform the PI of scores <95% for supervisory/training purposes. The PI will review 25% and therapists will review 25% of each other's sessions for ongoing training/supervision. Only consultant reviews will be used to assess fidelity.

2. Treatment Receipt

To ensure treatment comprehension, participants will be encouraged to ask questions. Workbooks describe and reinforce treatment content. To assess treatment receipt, participants will complete a brief quiz at end of Session 4.

3. Treatment Enactment

To ensure home assignments are done, workbooks contain written instructions on home assignments. To assess enactment, participants will maintain daily electronic diaries and logs.

Treatment Credibility and Expectancy

At the end of Session 3, participants will complete a treatment credibility questionnaire. This 4-item scale assesses the participant reaction to therapist and treatment efficacy, and participants provide ratings of 1 (strongly disagree) to 10 (strongly agree). Higher scores represent better treatment credibility. At the end of session 3 therapists will complete an expectancy for improvement scale.

Outcomes

A summary of study outcomes is provided in Table 3 and a schedule of outcome measures is provided in Table 4. A full description of the thermal pain task conducted during fMRI scanning is provided in Table 3. Briefly, for this task, the thermal stimuli will be delivered with an MR compatible, computer-controlled, CHEPS Pathway system, which is a peltier-element-based stimulator, which is capable of producing stimuli across a range of temperatures (33__ºC –51ºC). The start of each scan will begin with the thermode on the left foot at ambient temperature for 42s and then 16 cycles of the following: the pain temperature (determined by the calibration trials), and remain at that temperature (hold) for 5-seconds, followed by a variable inter stimulus interval with an average between 10-12 seconds. Following the 16th cycle, the scan proceeds for another 30s with the thermode at ambient temperature. After each scan, participants will report the average and max pain rating during the scan.

Study Timeline

The study timeline is provided in Table 5.

Analytical Approach

Power Analysis

Effect sizes in our prior trial that were small for pain (*f*=.2), medium to large for sleep (*f*=.31-39), large for imaging (*f*=.69-1.13), and large for pain- and sleep-related cognitive-affective arousal (*f*=.69-1.13). To ensure adequate power with an active control, effect sizes from CBT-I trials in fibromyalgia with SH control groups were considered and ranged from small to medium for pain (*f* =.15-.25; including pain-related anxiety) and small to large for sleep outcomes (*f*=.15-.40).[3,4] Our prior trial did not measure peripheral arousal. However, based on prior research,[7] small to medium effects (*f*=.15-.25) are expected. We determined power based on the traditional RM-ANOVA approach, as there are no established procedures for accurate power estimation for Multi-level Modeling (MLM). Using G-Power[58] for RM ANOVA within-between interaction, setting α=.05, number of groups=2, number of measurements=4, and correlations between repeated measures=.5, minimum statistical power=.8, the sample size required to detect a small effect of *f* =.15 is 62. For the mediation model tested in Aim 4, given that the ESs of the mediating paths range from small to large (*f*=.15 to .40), a sample size of 130 provides sufficient power (>.8) to detect the mediation effects on pain.[59]

Missing Values

Missing data will also be accounted for using MLM. This statistical procedure can handle missing data at all levels except the highest, which in our case, is level 2. When collecting measurements from the same people over time, some may not complete the study. Unlike RM ANOVA which would exclude these participants' data from analysis, with MLM, their information is retained in the prediction model which increases statistical power. Additional steps will be followed: 1-group dropout rates will be compared using chi-square analyses, 2-demographic and dependent variables will be examined for relationship to dropout, using related

variables to impute missing values in analyses below (via SPSS Missing Items Analysis), 3-comparison of completers vs. imputated analyses to further estimate dropout effects.

Baseline demographics and participant characteristics

Group differences in baseline demographics and clinical characteristics will be analyzed using independent sample t-tests for continuous variables (number of health conditions, BMI, Mini Mental State Examination, duration of fibromyalgia, duration of insomnia) and chi-square analyses for categorical variables (sex, marital status, ethnicity, employment status, sleep or pain medication usage). Any variables that are significantly different between groups will be entered in all analyses. We will also include age and education in all analyses as necessary.

Evaluations of Aims

Testing of Aim 1

To examine the effects of CBT-I on arousal, sleep, and pain in patients with fibromyalgia and insomnia, we will use a 2-level MLM. The first level will be the repeated measure over time nested within the second level which is the person-level data. Group (CBT-I, SH) will capture the between subjects variability, while time (baseline, post-treatment, 6 months, 12 months) will capture within-subject variability. Based on a priori hypotheses, separate MLMs will be conducted for each sleep, arousal, and pain outcome. Planned contrasts will be conducted consistent with a priori hypotheses. Bonferroni adjusted p-values will control family-wise error (FWE). Using a MLM approach allows us to not only compare group means like in a RM ANOVA, but also make comparisons at the individual level. Using an MLM approach, we can answer questions such as: do participants differ at specific time points on the outcome in terms of treatment, do slopes differ in terms of treatment or across participants, do specific time points vary among individuals. MLM allows for comparison of individual trajectories and comparisons between participants.

Clinical significance will also be evaluated for insomnia and pain intensity. Because there are no established clinical significance guidelines for insomnia, participants will be classified as no longer meeting trial criteria for difficulties initiating and maintaining sleep [i.e., self-reported sleep onset latency (SOL) or wake time after sleep onset (WASO) > 30 minutes on 3 or more days out of 14) at post-treatment, 6-month follow-up, and 12-month follow-up. We will also compare responders (those who no longer meet criteria for insomnia) vs. non-responders (those who still meet criteria for insomnia) on all outcomes using independent sample t-tests. In terms of pain, participants will be classified as moderately and substantially improved (pain intensity decreases of 30%, and 50%, respectively) based on provisional benchmarks recommended for determining clinically important differences in pain intensity in clinical trials by the IMMPACT (Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials) Consensus Panel.[60] These improvement benchmarks will be examined for both morning and evening pain intensity. Group differences will analyzed using chi-square.

Testing of Aim 2

Resting State

To better understand the effects of treatment on basal brain activity, we will characterize the changes in resting state (RS) data associated with behavioral changes over time. Toward this end we will use GIFT to perform independent component analyses (ICA) of the RS data. This procedure will decompose the data into discrete components, each representing the unique time course of the brain regions associated with that component (i.e., a unique spatial-temporal map). This analytic approach will allow us to identify common (across all groups) and group specific temporal-spatial ICAs representing the DMN, its subnetworks, pain-related networks, those involved with affective processing and others (e.g. sensorimotor networks, saliency network,

frontoparietal executive networks etc.). Once identified, GIFT will then be used to test for changes in the effective connectivity and functional coherence among these networks and their component brain regions. Then the influence of covariates can then be added to the analyses to examine their influence on specific nodes and overall functional coherence of the network. We will also compare the component representative of the DMN (i.e., a specific spatial-temporal map) from each group to a study specific DMN map to calculate group specific differences. By comparing these differences to a standardized DMN template (of healthy controls that is included in GIFT), we can make statistical inferences about group related differences and treatment related changes over time. Although the standardized template of the DMN included with GIFT is widely used, we acknowledge the limitations of using this template because it is based on healthy individuals (Please see Franco, Pritchard, Calhoun, & Mayer, 2009[61] for more information). However, the fact that this template is based on a healthy population, valid inferences about deviations from a normal DMN in a clinical population are possible.

Using the approach outlined above we anticipate that the component best representing the DMN in both groups will include most, if not all of the following Brodmann areas: BA 11 - Orbitofrontal area (orbital and rectus gyri), BA 32 - Dorsal anterior cingulate cortex, BA 9 - Dorsolateral prefrontal cortex, BA 10 - Anterior prefrontal cortex (most rostral part of superior and middle frontal gyri), BA 47 - Orbital part of inferior frontal gyrus, BAs 23 & 31 the ventral and dorsal aspects of the posterior cingulate cortex, BA 39 - Angular gyrus, BA 40 - Supramarginal gyrus, BA 37 - Fusiform gyrus, and BAs 30 & 36 of the parahippocampal gyrus. Because participants have chronic pain we expect overlapping pain-related regions to be included (e.g., BAs 40, 30, 31). However, given the tonic nature of chronic pain, we expect the DMN might also

involve additional pain-related brain regions such as: BAs 4 - primary motor cortex, 6 - premotor cortex, 16 - insular cortex, and 46 - dorsolateral prefrontal cortex.

fMRI

Using a flexible analytical approach involving Multilevel Modeling (MLM) and Random Effects General Linear Models (RFX-GLMs) we will test for group differences in reported pain and associated pain-related patterns of activity and how those results vary as a function of treatment response and time. To clarify treatment related changes to painful stimuli we will identify brain regions of interest (ROIs) wherein the stimuli are significantly convolved with a hemodynamic response function (HRF). When identifying potential ROIs, a combination of criteria are used to guard against Type-I errors. These criteria are: A) p-value ≤ 0.05, using the false discovery rate (FDR) and family wise error (FWE) corrections; B) a spatial-extent of 50+ contiguous voxels and a minimum volume of 100μL; and C) the center of mass-gravity/peak voxel in a targeted region. Because all of the imaging data will be in standardized MNI space, the coordinates of targeted regions will be checked against the standardized Wake Forest Pick Atlas. The combination of these criteria establish an image-wise p-value of 0.00002 and an effective pixel-wise alpha of $p \leq .0002$.[62] This approach will allow us to include additional criteria such as small volume corrections during analyses which may also include Area under the curve, growth curve modeling and cluster analyses may also be used to test for group related differences, over time, in HRF characteristics relative to treatment response, and the predictive ability of outcome measures. With the aforementioned analytical approach we anticipate to identify pain-related activity among typical pain-related brain regions such as: the thalamus, supplementary motor area, primary and secondary somatosensory cortices, anterior and posterior insula, dorsal anterior cingulate cortex, and the dorsolateral prefrontal cortex. We hypothesize that these, and other pain-

related, regions will not only be identified at baseline, but that they will be sensitive to treatment effects and changes in other behavioral outcome measures (e.g., sleep measures, pain, arousal, etc.) over time.

Testing of Aim 3

Structural MRI

To study CBT-I's long-term effect on structural characteristics of pain-related brain regions, we will use the FSL tissue segmentation pipeline for analysis of cortical ribbon changes. The FreeSurfer Longitudinal Processing pipeline is highly specialized to provide unbiased results about longitudinal changes using common and within subject templates, allowing for significant increases in reliability and statistical power.[63] The pipeline accounts for inherent auto correlations in the data due to repeated sampling allowing us to assess changes among outcome measures (e.g., arousal, sleep, pain, and gray matter thickness, in ROIs) within/between groups at each interval and longitudinally. Based on the literature[39 40 64-67] and our previous results, we anticipate finding significant differences between the CBT-I and SH groups among the somatosensory cortices, cingulate cortices (anterior, mid-dorsal), dorsolateral prefrontal cortex, frontal gyri (superior, middle, inferior), insula (anterior, posterior), temporal gyri, thalamus, and periaqueductal gray and their relationship to additional outcome variables. Other behavioral and/or outcome measures refers to possibility of using any other information collected about the participants (e.g., sleep measures, pain, arousal, etc.).

Diffusion Weighted Imaging (DWI)

The diffusion weighted images will be processed via FMRIB's Diffusion Toolbox (FDT) to examine white matter characteristics diffusion weighted images. DWI measures the diffusion of water across cell membranes in 3D. Because of this, the directionality of the diffusion

(anisotropy), can be determined. The FDT pipeline will estimate the apparent diffusion coefficient (ADC - amount of diffusion possible independent of direction) and fractional anisotropy (FA - an index (0 [isotropic diffusion] - 1 [diffusion along one vector]) at the individual and group levels. Higher values of FA and reduced ADC represent increased complexity of brain tissue.[68 69] Higher values of FA and reduced ADC represent increased complexity of brain tissue.[68 69] We will map white matter tracts and model connections among brain regions with probabilistic tractography.[44 70 71] As this will be a novel contribution to the field we anticipate potential changes for CBT-I but not SH in FA and ADC along the prefronto-subcortical dorsolateral-prefrontal and anterior cingulate-prefrontal pathways.

Testing of Aim 4

Finally, to examine the mediating impact of arousal, sleep, and CS on the effects of CBT-I on pain (Aim 4), we will use 4-wave cross-lagged path analysis. Controlling for baseline, autoregressions, and reciprocal effects among sleep, arousal (HRV, cognitive arousal, stress), and CS (neural factors), we will examine whether CBT-I continues to predict improved sleep and decreased arousal and CS at 6 months, and then predicts pain at 12 months. Mediation effects of arousal, CS, and improved sleep of impact of CBT-I on pain outcomes at 12 months will be estimated. We will evaluate whether mediation effects remain significant after controlling for global and pain- and sleep-specific cognitive-affective variables.

Patient and Public Involvement

Patients and public are not involved in any of the following study procedures: development of research questions and outcome measures, study design, participant recruitment, plan for results dissemination, assessment of burden of intervention.

Ethics and Dissemination

All study procedures were approved by the Institutional Review Board at the University of Missouri on July 11th 2018. An independent 4 member Safety Monitoring Committee (SMC) was assembled in January 2019 to oversee the study. Members include those with expertise in fibromyalgia, chronic insomnia, sleep medicine and CBT. All SMC members attested that they have no conflicts of interest. The SMC met once via conference call at the beginning of the study to review the study protocol, Manual of Operating Procedures (MOOP), Informed Consent Form, and monitoring plan with emphasis on data integrity and patient safety issues. Following this initial meeting, the SMC will meet every 6 months to review progress reports prepared by the team biostatistician. Those SMC reports will include interim statistical analyses. Any changes to these procedures that are recommended by the SMC will be adopted. The SMC will review adverse events and monitor study results, focusing on efficacy, recruitment progress, randomization, compliance, retention, protocol adherence, operating procedures, forms completion, intervention effects, participant safety, and minority inclusion. The PI registered the study within ClinicalTrials.gov (NCT03744156) on November 16th, 2018. The PI will also submit annual reports to the funding agency.

Results from this trial will be presenting at national conferences, including the Associated Professional Sleep Societies (APSS or SLEEP) and the American Pain Society, in the final year of the project. Dissemination will also occur through the submission of a primary article on the outcomes, a second article focusing on the functional neural changes (i.e., resting state and fMRI results), a third article focusing on the structural neural changes, and a fourth focusing on outcome mediation. The treatment materials will be shared electronically and will be widely available to clinicians.

Table 1. Session Content for CBT-I

Session Number	Content
1. Sleep Education	Participants will be provided with education on sleep stages; sleep and fibromyalgia; and circadian rhythms and sleep. This information is given to provide a heuristic background for the specific sleep techniques used.
2. Sleep Hygiene (SH)	SH will be discussed and participants are instructed to adhere to the following rules: 1-Avoid caffeine after noon, 2-Within 2 hours of bed, avoid exercise, nicotine, alcohol, and heavy meals, 3-Within 1 hour of bedtime, avoid screen time. The goal of SH is to eliminate sleep-interfering behaviors.
3. Stimulus Control (SC) & Brief Relaxation	SC will be discussed and participants will be asked to adhere to the following recommendations: 1-Do not use bed/bedroom for anything but sleep (or sex), 2-If not asleep in 15-20 mins, leave bed, do something non-arousing in another room. Return to bed when sleepy. If not asleep in 20 mins, repeat., 3-If awake & not back asleep in 20 mins, repeat #2, 4-Avoid napping. The goal of SC is to break incompatible/build compatible sleep associations. In addition, a 10 min relaxation exercise will be recorded and given to participants for practice at bedtime & once during the day. The goal of this is to induce relaxation/reduce arousal.
4. Sleep Restriction	A time in bed prescription (Rx) will be set at baseline average diary reported total sleep time plus 30 mins. If this value is <5 hrs, Rx will be set at 5 hrs. The therapist and participant will work together to set regular bed/wake times consistent with Rx. The goal of sleep restriction is to regulate sleep-wake cycle and reduce awake time in bed.
5. Monitoring Automatic Thoughts	Thoughts, thought patterns and emotional reactions that interfere with getting good

	sleep (i.e., “I will never sleep well again.”) will be identified and monitored.
6. Challenging/Replacing Dysfunctional Thoughts	The validity of sleep-interfering thoughts will be challenged and replaced with sleep conducive ones (i.e., “There are things I can do to improve my sleep.”)
7. Practical Recommendations	Established cognitive restructuring techniques (i.e., reappraisal, reattribution, and decatastrophizing) will be taught.
8. Review and Maintenance	Learned skills and importance of a regular sleep schedule and good sleep habits will be reviewed. Continued use of the techniques learned will be discussed.
Booster Sessions	In this brief (~20 mins) telephone session, techniques from Session 1-8 will be reviewed. The therapist will encourage continued practice of techniques. Problems will be trouble-shooted.

Table 2. Session Content for SH

Session Number	Content
1. Sleep Education	Content is the same as CBT-I
2. Sleep Hygiene (SH)	Content is the same as CBT-I.
3. Insomnia and Pain	Participants are provided education on chronic/acute insomnia (Spielman's 3 P's Model)[53] and the Gate Control Theory[54] of Pain.
4. Environment	Participants are provided with education on SH rules related to environmental factors (e.g., noise, light).
5. Lifestyle	Participants are provided with education on lifestyle factors that influence sleep (e.g., use of stimulants & other substances).
6. Diet	Participants are provided with education about diet and nutrition and their influence on sleep.
7. Exercise	Participants are provided with education about exercise and its influence on sleep.
8. Review and Maintenance	In the final session, SH training reviewed and continued practice is encouraged. Problems are trouble-shooted. All education provided in previous sessions will be reviewed. Finally, continued engagement in education will be discussed.
Booster Sessions	As in CBT-I, all training and education covered in SH training will be reviewed in a brief (~20 mins) telephone call. Continued SH practice and education engagement are encouraged. Problems are trouble-shooted.

Table 3. Outcome Measures

Outcome Category	Measure	Primary/Secondary	Details
Subjective Sleep	Daily Sleep Diaries	Primary	Online diaries will be completed each morning (~5 mins) during each 2 week assessment period and 8 weeks of treatment. Primary outcome variables include: sleep onset latency (SOL; time from initial lights-out until sleep onset), wake after sleep onset (WASO; time awake after initial sleep onset until last awakening), number of awakenings, total sleep time, sleep efficiency (total sleep time/time spent in bed × 100), and sleep quality rating (1-very poor to 7-excellent). Sleep and pain medication consumption variables will include: name, dosage, and time taken. Sleep medication will be converted to number of lowest recommended dosage (LRD) units,[72] and pain medication to morphine equivalent dosage (MED).[73]
	Insomnia Severity Index (ISI)	Primary	At each time point, participants will complete the ISI (primary outcome).[74] The ISI is a seven item questionnaire that assesses the frequency and/or severity of insomnia symptoms [e.g., "rate the current severity of your difficulty falling asleep"; choices range from 0 (none) to very severe (5)], as well as questions regarding the impact of insomnia on daytime functioning [e.g., "to what extent do you do you consider your sleep problem to interfere with your daily functioning (e.g. daytime fatigue, mood, ability to function at work/daily chores, concentration, memory, mood, etc.) currently?; choices range from 0 (not interfering at all) to 5 (very much interfering). Total scores on the ISI range from 0-28, with higher scores representing more severe insomnia.
Objective Sleep	Daily Actigraphy	Secondary	Actiwatch 2® (Philips Respironics) is a watch-like device that monitors light and gross motor activity. Data will be analyzed by proprietary software using 30s epochs. A validated algorithm estimates the same variables (secondary outcomes) provided by diaries (except sleep

			quality). Participants wear the device 24/7 during each 2 weeks of assessment, and 8 weeks of treatment.
	Polysomnographic Sleep	Secondary	The Comet-PLUS® Portable (Natus Neurology) Recording System will be used to conduct a single in-home overnight sleep study at baseline, post-treatment, and both follow-ups. Consistent with ambulatory recommendations,[75] monitoring consists of 10 EEG, 2 EOG, and 3 EMG (chin) using standard placement, also includes respiratory inductance plethysmography (thoracic/abdominal effort), oximeter (pulse/oxygen saturation), electrocardiogram (ECG), R/L anterior tibialis EMG, oral-nasal airflow thermocouple, and nasal cannula pressure transducer. We require 4 hrs of acceptable data (i.e., scorable stage/respiratory events) and follow Sleep Heart Health Study (SHHS)[76] procedures for training, data management, and scoring. PSG provides sleep stage % (stage 1, 2, 3, Rapid Eye Movement Sleep) and absolute values for diary variables (secondary outcomes).
Arousal	Peripheral Arousal – Heart Rate Variability (HRV)	Primary	Using Holter monitors, we will obtain 5 minute electrocardiogram recordings during rest in a quiet controlled environment at each assessment. Time and spectral analysis of the short-term variability of HR will be performed using Pathfinder (Spacelabs, Seattle, WA) software to assess the neural regulation of HR. The time domain indices reflect the beat-to-beat variability with respect to time. The variables standard deviation of the N-N intervals (SDNN) and the percentage of N-N intervals that exceed 50 ms (pNN50) will be examined. The frequency domain indices reflect the underlying rhythms of the mechanisms modulating heart rate. High frequency (0.15-0.4 Hz), low frequency (0.04-0.15 Hz), and very low frequency (below 0.04 Hz) spectral bands will be examined.
	Global Cognitive Arousal-Perceived Stress Scale (PSS)[77]	Primary	The PSS (primary outcome) is a 10 item questionnaire that asks participants to appraise their stress level during the past month in response to several everyday situations (e.g., "in the last month how

			often have you been able to control irritations in your life?"). Choices range from 0 (never) to 4 (very often). Higher total scores on the PSS indicate worse perceived stress.
	Insomnia-Specific Cognitive-Affective Arousal - Dysfunctional Beliefs and Attitudes about Sleep (DBAS)[a]	Primary	The DBAS[74] is a 30 item scale that assesses the degree to which an individual agrees with statements regarding sleep (e.g., "Medication is probably the only solution to sleeping problems", "I need 8 hours of sleep to feel refreshed and function well during the day"). Participants rate their belief in each statement from 0 (strongly disagree) to 10 (strongly agree). Scores for each item are summed and higher scores on the DBAS indicate worse cognitive affective arousal related to insomnia.
	Pain-Specific Cognitive-Affective Arousal-Catastrophizing-Pain Catastrophizing Scale (PCS)[78]	Primary	The PCS is a 13-item scale that measures the degree (from 0-not at all to 4-all the time) to which participants experienced certain thoughts or feelings during past painful events. Items are scored and total scores on the PCS represent worse pain catastrophizing.
Pain	Daily Clinical Pain-Electronic Daily Diaries	Primary	On the daily electronic diaries, participants provide ratings on a 0-100 scale regarding their pain intensity (0-no pain sensation, 100-most intense pain imaginable) and pain unpleasantness (0-not at all unpleasant, 100-most unpleasant imaginable).
	Subjective Pain-McGill Pain Questionnaire (MPQ)[79 80]	Secondary	The MPQ assesses participants pain symptoms across 21 categories. For each category, participants select the best word that described their pain. Qualitative responses are coded by numerical value (e.g., 1-3 or 1-5), with higher values representing worse pain in that category. If they do not experience a specific category of pain, they do not provide a response to that category. Category scores are summed and total scores could range from 0 (no pain) to 78 (severe pain).

	Patient-Centered Outcomes Ques. (PCOQ)[81]	Secondary	The PCOQ is a 5-item questionnaire that assess on a 0-10 point scale usual levels of pain, desired levels of pain, what level of improvement in treatment outcomes they would consider successful, what level of improvement in treatment outcomes they expect after treatment, importance of improvement in treatment outcomes.
	Pain-Related Disability-Pain Disability Inventory (PDI)[82 83]	Secondary	The PDI includes 7-items rated on an 11-point scale (0 = no disability, 10 = total disability) indicating the degree to which chronic pain interferes with participant functioning in the following areas: family/home responsibilities, recreation, social activity, occupation, sexual behavior, self-care, and life-sustaining activity. The seven ratings are summed to compute a total score (0-70), with higher scores indicated worse pain disability.
Mood	State Trait Anxiety Inventory (STAI)[84]	Covariate	STAI asks respondents to rate how true self-descriptive statements (e.g., I feel calm) are on a 4-point scale (1 = not at all, 4 = very much so). Typically, respondents are asked to rate statements according to how they generally feel (trait-anxiety scale) and how they feel in the current moment (state-anxiety scale). Total scores range from 20 to 80, with higher scores indicating greater maladjustment.
	Beck Depression Inventory – 2nd Edition (BDI-II)[85]	Covariate	The BDI-II contains 21 items that measure the severity of depressive symptomatology on a three-point scale (0 = absence of symptoms, 3 = most severe). Typically, respondents answer for the previous week, but the previous two weeks were used in this study to match the two-week activity recording period for each assessment. Total scores range from 0 to 63. Ranges for clinical levels of depression are 0 to 13 (minimal), 14 to 19 (mild), 20 to 28 (moderate), and 29 to 63 (severe).
	Pain Anxiety Symptoms Scale (PASS-20)[86]	Covariate	The PASS measures fear and anxiety responses related to pain. The PASS-20 revised short form version contains 20 items in which participants must rate the frequency in which they experience fearful and anxiety ridden responses related to pain or pain-related situations.

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			This scale is widely used in clinical screening of chronic pain and pain research.
	Anxiety and Preoccupation about Sleep Questionnaire (PSQ)[87]	Covariate	The APSQ measures the intensity of both daytime and nighttime worry related to insomnia. Participants are presented with 10 statements describing several sleep related worries and participants are asked to indicate how true they on a scale from 1 (not true) to 10 (very true). Scores on this scale are associated with self-reported (e.g., diary) sleep measures as well as daytime impairment, with higher scores representing worse anxiety related to sleep.
Neuroimaging	Neural Plasticity and Central Sensitization	Primary	Three imaging protocols, 1) structural MRI (MPRAGE), 2) functional MRI (EPI BOLD), and 3) Diffusion Weighted Imaging (DWI), will assess neural plasticity and central sensitization. Image acquisition Imaging data will be acquired with Siemens' new MAGNETOM Vida 3T and a 20-channel head-neck coil. The parameters for the 3D-T1-weighted structural scans are: 256 axial slices (.90*.89*.89mm3; TR=.75s, TE=0.0045s, flip angle=75°, matrix=256*256, FOV = 256mm. T2 gradient EPI sequence for the resting state and fMRI scans will use the following parameters: whole brain, 36-contiguous slices (axial), 3mm3 isotropic voxels, oriented parallel to the AC-PC plane, TR=2.46s; TE=30ms; flip angle=90◦; 76*76 matrix, and 120 volumes. The parameters for the diffusion weighted scans are: 32 slices, 1*1*3.25mm2, TR=3.6s, TE=.064s, Flip angle = 90º, directions=6. The sequence of scan acquisition is: Localizer, gradient field map, 3D anat, resting state (x2, ~5 mins), fMRI experimental pain scans (x3, ~25 mins), DTI (~12 mins). During the resting state scans, subjects are told to relax, limit movement, and try not to fall asleep. In preparation for the experimental pain scan, participants will first undergo quantitative sensory testing (QST) calibration trials outside of

the scanner, in order to determine individual pain tolerance and to ensure that experienced pain intensity is equal in both treatment groups at baseline. A computer-controlled Medoc Pain and Sensory Evaluation System (Pathway Model ATS, Medoc Advanced Medical Systems, Durham, NC) will be used to deliver thermal stimuli. QST calibration uses a series of calibration trials (CTs) to identify their pain tolerance temperature, which will be used during their experimental pain scanning session. The CTs start at 43ºC and increase by 1ºC until their tolerance, or 51ºC is reached, whichever comes first. Subjects will sit in a chair, remove their shoes and socks, and extend their feet outward. A researcher will wipe the bottom of the foot with an alcohol pad, after which a contact heat thermode will be placed on the plantar surface of the foot. Each stimulus cycle is initiated by the experimenter via key press. After each stimulus, subjects will describe the sensation (pain/not painful) and rate its pain intensity on a scale from 0–no pain to 100–worst pain imaginable. Once the ratings and inter-stimulus interval have finished the cycle will be repeated until their tolerance temperature is identified (i.e., the lowest temperature with a pain intensity rating of ≥ 65). This will be the temperature that will be used during their scanning sessions

During each 5 min. experimental pain scan, thermal stimuli will be delivered with an MR compatible, computer-controlled, CHEPS Pathway system, which is a peltier-element-based stimulator, and is capable of producing stimuli across a range of temperatures (33ºC – 51ºC). The start of each scan will begin with the thermode at ambient temperature for 30s and then 16 cycles of the following: 12s at ambient temperature, then in less than two seconds the temperature will steadily increase (ramp) until reaching their pain temperature (determined by the calibration trials), and remain at that temperature (hold) for 5-seconds, followed by a variable inter stimulus interval of 12-20 seconds. Following the 16th cycle, the scan proceeds for another 30s with the thermode at ambient temperature.

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[a]Given that our previous clinical trial[20] evaluating CBT-I relative to a waitlist control on sleep and pain and arousal outcomes found large effect sizes for CBT-I related improvement in DBAS-assessed cognitive-affective arousal related to sleep, we used the same measure in this trial as well. However, another important index of pre-sleep arousal (including somatic and cognitive arousal) could be captured by using the Pre-sleep Arousal Scale (PSAS)[88]. Thus, we will consider using the PSAS in future trials.

Table 4. Schedule of Outcome Measures

Assessment Period	Base	Tx	Post	Boosters	FUs
Weeks	**2**	**8**	**2**	**2**	**2**
Telephone & clinical interviews, consent, MMSE	X				
Actigraph, PSG, ISI, MPQ, PDI, RH, Wind-Up, HRV, DBAS, PSS, PCS, STAI, BDI-II, PASS-20, APSQ	X		X		X
Electronic Daily Diaries	X	X	X	X	X
Tx Integrity – Delivery & Receipt, Treatment Credibility		X			

Note. MMSE = Mini Mental State Examination; PSG = Polysomnography; ISI = Insomnia Severity Index; MPQ = McGill Pain Questionnaire; PDI = Pain Disability Inventory; RH = Ramp and Hold; HRV = Heart Rate Variability; DBAS = Dysfunctional Beliefs about Sleep Scale; PSS = Pain Severity Scale; PCS = Pain Catastrophizing Scale ; STAI = State Trait Anxiety Inventory; BDI-II = Beck Depression Inventory – 2nd Edition; PASS-20 = Pain Anxiety Symptoms Scale; APSQ = Anxiety and Preoccupation about Sleep Questionnaire

Table 5. Study Timeline

Project Year→	1		2		3		4		5	
Half →	1	2	1	2	1	2	1	2	1	2
1. Develop Manual of Operating Procedures. Register with clinicaltrials.gov. Publish trial protocol. Develop SH. Train therapists & assessor.	■									
2. Recruit, collect baseline, deliver treatment		■	■	■	■	■	■			
3. Collect post-treatment assessment				■	■	■	■	■		
4. Collect 6 & 12 month follow-up assessments			■	■						
5. Offer/provide CBT-I to SH controls									■	
6. Final data analysis & dissemination (continues after grant ends); final report									■	■

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Contributors

All authors made substantial contributions to the concept and design of the study. CSM drafted initial protocol, with input from all authors. JCG, RS, MR drafted MRI protocol. CBD drafted statistical analysis plan. CSM, PS and CS drafted screening procedures. CSM and AFC drafted the manuscript. All authors revised the manuscript.

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Disclaimer

The study sponsor was not actively responsible or involved in the study design and will have no involvement in collection, management, analysis or interpretation of data. The sponsor will have no involvement in future manuscript preparation and decision to submit for publication. This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Competing Interests

None declared.

Ethics approval

The study and methods were evaluated and approved by the Institutional Review Board at the University of Missouri (IRB Project Number: 2011835).

Provenance and peer review

Externally peer reviewed at the NINR at the NIH.

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List of Figures

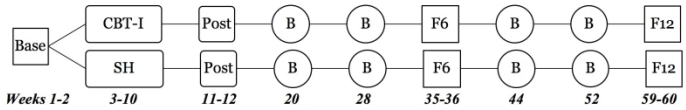

Figure 1. Timeline of Randomized Controlled Trial

215x279mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Check (x)	Description
			Administrative information
Title	1	x	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a	x	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	x	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	x	Date and version identifier
Funding	4	x	Sources and types of financial, material, and other support
Roles and responsibilities	5a	x	Names, affiliations, and roles of protocol contributors
	5b	x	Name and contact information for the trial sponsor
	5c	x	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	x	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction			
Background and rationale	6a	x	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	x	Explanation for choice of comparators
Objectives	7	x	Specific objectives or hypotheses

Trial design	8	x	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
			Methods: Participants, interventions, and outcomes
Study setting	9	x	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	10	x	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11a	x	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	x	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	x	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	x	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12	x	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	13	x	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14	x	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15	x	Strategies for achieving adequate participant enrolment to reach target sample size
			Methods: Assignment of interventions (for controlled trials)
Allocation:			

Sequence generation	16a	x	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
Allocation concealment mechanism	16b	x	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	x	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a	x	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	x	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
			Methods: Data collection, management, and analysis
Data collection methods	18a	x	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b	x	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	x	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a	x	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b	x	Methods for any additional analyses (eg, subgroup and adjusted analyses)

	20c	x	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
			Methods: Monitoring
Data monitoring	21a	x	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
	21b	x	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22	x	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23	x	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
			Ethics and dissemination
Research ethics approval	24	x	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	25	x	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a	x	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	x	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	x	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	28	x	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29	x	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators

Ancillary and post-trial care	30	x	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	x	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	x	Authorship eligibility guidelines and any intended use of professional writers
	31c	x	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices			
Informed consent materials	32		Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33		Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.