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SCIENTIFIC INVESTIGATIONS

Neural activation changes in response to pain following cognitive behavioral therapy for patients with comorbid fibromyalgia and insomnia: a pilot study

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Study Objectives: To examine whether cognitive behavioral treatments for insomnia (CBT-I) and pain (CBT-P) lead to neural activation changes in response to pain in fibromyalgia.

Methods: Thirty-two patients with fibromyalgia (mean age = 55.9, standard deviation = 12.2) underwent an experimental pain protocol during functional magnetic resonance imaging and completed 14-day diaries assessing total wake time, total sleep time, and pain intensity before and after CBT-I, CBT-P, or waitlist control. Random effects analysis of covariance identified regions with significant group (CBT-I, CBT-P, waitlist control) by time (baseline, post-treatment) interactions in blood oxygen level–dependent response to pain. Linear regressions using residualized change scores examined how changes in total wake time, total sleep time, and pain intensity were related to activation (blood oxygen level–dependent) changes.

Results: Twelve regions exhibited small to moderate effects with significant interactions *P*s < .00; right hemisphere: inferior frontal, middle occipital, and superior temporal gyri, insula, lentiform nucleus; left hemisphere: angular, superior temporal, midfrontal, inferior occipital, midtemporal, and inferior frontal gyri. Blood oxygen level–dependent response to pain decreased in 8 regions following CBT-I, and in 3 regions following CBT-P (CBT-I effects > CBT-P). Blood oxygen level–dependent response also increased in 3 regions following CBT-P and in 6 regions following waitlist control. Improved total wake time and/or total sleep time, not pain intensity, predicted decreased blood oxygen level–dependence in 7 regions (*P*s < .05), accounting for 18%–47% of the variance.

Conclusions: CBT-I prompted greater decreases in neural activation in response to pain across more regions associated with pain and sleep processing than CBT-P. Reported sleep improvements may underlie those decreases. Future research examining the longer-term impact of CBT-I and improved sleep on central pain and sleep mechanisms is warranted.

Clinical Trial Registration: Registry: ClinicalTrials.gov; Title: Sleep and Pain Interventions in Fibromyalgia (SPIN); Identifier: NCT02001077; URL: https://clinicaltrials.gov/ct2/show/NCT02001077

Keywords: fibromyalgia, insomnia, cognitive behavioral treatment, imaging, quantitative sensory testing

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BRIEF SUMMARY

Current Knowledge/Study Rationale: The brain's response to pain is often larger in patients with fibromyalgia compared to healthy controls and contributes to chronic pain complaints. The extent to which the brain's response to pain may be impacted by cognitive behavioral treatments for chronic pain and insomnia is unknown.

Study Impact: Results from the current pilot study suggest that cognitive behavioral treatments for insomnia (CBT-I) may prompt greater decreases in the brain's response to pain across more regions associated with pain and sleep processing than cognitive behavioral treatments for pain (CBT-P). Improved sleep may underlie those decreases. Over time, those decreases have the potential to reduce or eliminate chronic pain complaints in patients with fibromyalgia.

INTRODUCTION

Fibromyalgia is characterized by chronic widespread pain and heightened sensitivity to pain.[1] Central sensitization is the predominant pathophysiology of fibromyalgia and involves increased excitability of the spinal and supraspinal neurons,[2] which leads to hyperalgesia and mechanical allodynia.[3] Hyperalgesia refers to increased sensitivity to pain, while mechanical allodynia refers to pain in response to stimuli that healthy individuals do not consider painful. Sustained arousal across the pain matrix[4] contributes to sustained pain sensitivity in fibromyalgia. Wind-up is a common experimental model for studying central sensitization and the neuroplastic changes that contribute to chronic pain. Wind-up is also known as temporal summation of second pain and refers to the increase in pain that occurs in response to repeated stimuli and the subsequent after-sensations. Research indicates wind-up is a clinically relevant manifestation of central sensitization and chronic pain.[5] It results from

repetitive activation of C-fibers in neurons of the dorsal horn and occurs when the frequency of stimulus repetition is greater than or equal to 0.33 Hertz.[6,7] Wind-up is prolonged in patients with fibromyalgia compared to healthy controls.[6] Importantly, hyperalgesia, mechanical allodynia, and enhanced wind-up are predictors of clinical pain intensity in individuals with fibromyalgia.[8]

More than 50% of individuals with fibromyalgia also report chronic insomnia.[9,10] Research supports a bidirectional relationship between sleep and pain such that disturbed sleep is more commonly a determinant of pain rather than a byproduct.[11] A review of longitudinal, microlongitudinal, experimental, and clinical trial data by Finan and colleagues[12] concluded that there is greater support for the impact of sleep on chronic pain than vice versa. Interest in sleep as an influence on pain has prompted examination of the impact of cognitive-behavioral treatment for insomnia (CBT-I) on chronic pain. CBT-I is an established and highly efficacious treatment for insomnia.[13] In a meta-analysis of 11 randomized clinical trials of which 3 focused on fibromyalgia, Tang and colleagues[14] found that treatment involving CBT-I or at least 1 component of CBT-I improved sleep (standardized mean difference –0.68), pain (0.18), depression (0.24), and fatigue (0.38) in chronic pain populations. While growing evidence supports the impact of CBT-I on pain and sleep, the mechanisms through which this treatment improves pain and sleep in patients with fibromyalgia remain unclear.

The cognitive action theory of stress provides a theoretical framework linking chronic pain and insomnia to common neurophysiological pathways.[15,16] Given that chronic arousal has been linked to both disorders,[7,17] arousal may alter hypothalamic-pituitary-adrenal axis and central nervous system functioning consistent with the central sensitization seen in fibromyalgia.[18] Further support for this conceptual model comes from brain imaging studies. A resting state paradigm examining default mode network found that both fibromyalgia and insomnia are characterized by altered activity and connectivity patterns that are not typically observed in healthy persons.[7,19,20] It is possible that these aberrant activity patterns can be changed through interventions that specifically target sleep and/or pain. Both are factors that may contribute to and maintain the chronic arousal that contributes to the abnormal neuroplasticity and central sensitization observed in fibromyalgia. We previously reported that in patients with fibromyalgia and relative to cognitive behavioral therapy for pain (CBT-P) or a waitlist control (WLC), CBT-I prompted structural plasticity involving increased cortical thickness in brain regions associated with pain processing.[20] While cortical atrophy is linked to both fibromyalgia and insomnia, its etiological role in these disorders is unclear. Thus, examination of potential functional plasticity, particularly changes in neural activation in response to pain following these behavioral interventions is warranted and has clearer etiological implications given the role of central sensitization in fibromyalgia.

In this pilot study, we examined whether CBT-I and CBT-P lead to changes in neural activation in response to pain in a subset of patients with comorbid fibromyalgia and insomnia from the Sleep and Pain Interventions (SPIN) trial.[21] In that trial, both treatments prompted clinically significant improvements in pain in about one third of patients. Likewise, both improved sleep. However, the magnitude of improvements was greater for CBT-I. Based on those findings, our finding of greater structural plasticity following CBT-I, and growing evidence suggesting sleep may play a greater role in chronic pain than the reverse, we predicted CBT-I would prompt reductions in neural activation in response to pain at post-treatment greater than CBT-P and WLC. Given the preliminary nature of this pilot research and the large number of regions involved in sleep and pain, we did not make hypotheses regarding which specific regions were expected to demonstrate activity reductions.

METHODS

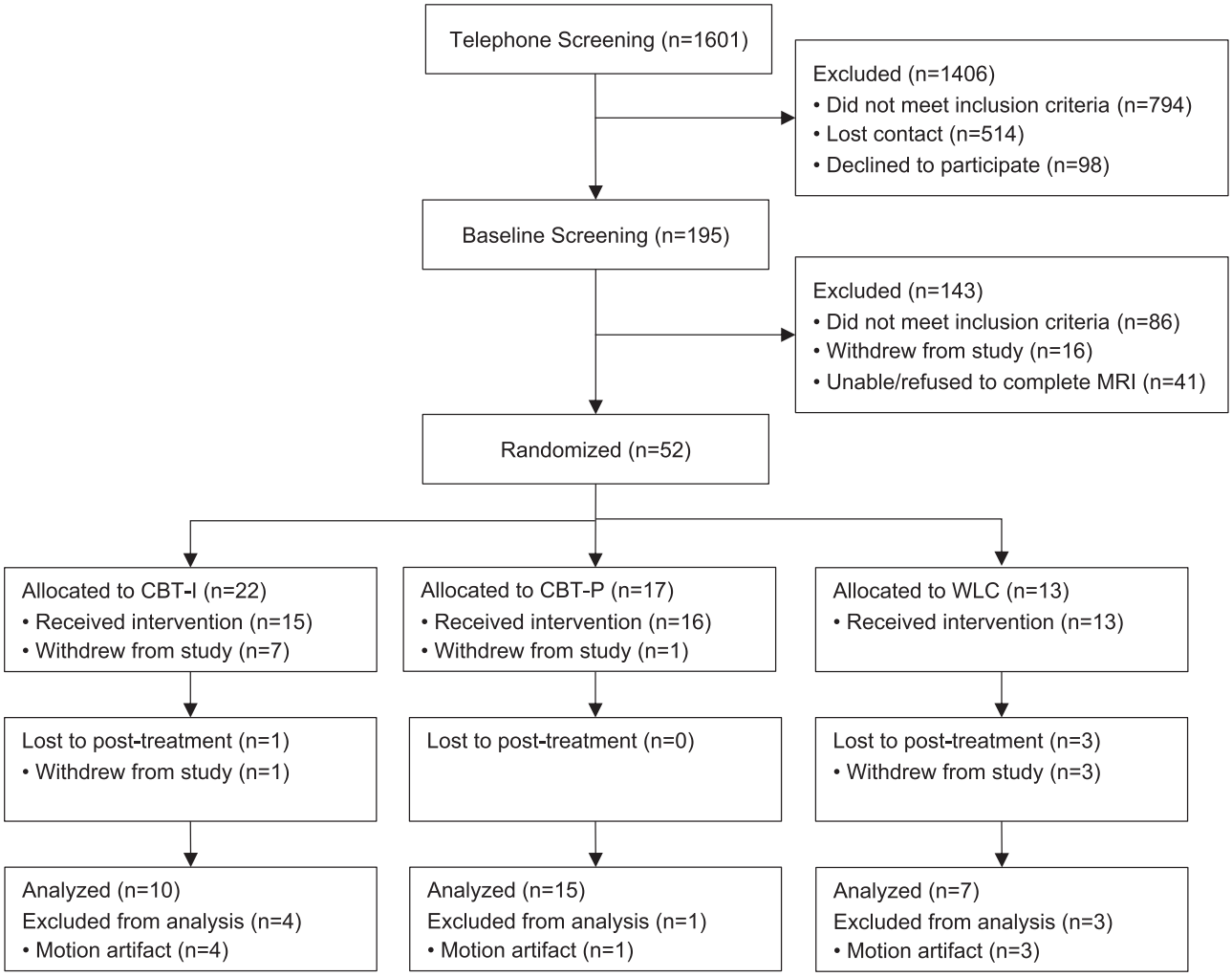
Participants

This analysis used data from a larger clinical trial (NCT02001077) that investigated the efficacy of CBT-I and CBT-P for treating sleep and pain symptoms associated with fibromyalgia.[21] In the parent study, individuals with fibromyalgia were recruited from the community between 2009 and 2012. A subset of these participants (n = 32) underwent an experimental pain protocol involving thermal stimuli during functional magnetic resonance imaging (fMRI) scanning before and after 8 weeks of treatment. The collection of neuroimaging data was supported by a supplemental grant that started 6 months after the start of recruitment for the parent study. The Consolidated Standards of Reporting Trials diagram for the present analysis (**Figure 1**) does not include the 234 individuals who inquired about the study during the first 6 months of recruitment, as they did not have the opportunity to participate in the fMRI portion of the study. Participants in the analysis sample for this paper were predominantly female (95%) with an average age of 55.9 years (SD = 12.2). A majority of the sample were Caucasian (86.5%), with the remaining identifying as either African American (10.8%) or Native American (2.7%). Latino ethnicity was endorsed by 8.1% of the participants. Baseline demographic characteristics for each treatment group are presented in **Table 1**. The groups did not differ on baseline demographic and clinical characteristics (all *P*s > .05).

Individuals were eligible to participate in the parent study if they reported having fibromyalgia for at least 6 months and their symptoms were confirmed at intake by tender point testing using guidelines established by the American College of Rheumatology.[1] Included participants reported pain in at least 11 of 18 tender points, including points in all 4 body quadrants with application of a 4-kg force. The presence of insomnia was determined using standard research and diagnostic criteria: 1) individual reported sleep onset or awake time during the night > 30 minutes at least 3 nights per week for more than 6 months, 2) sleep diary confirmed sleep onset or awake time during the night > 30 minutes at least 6 nights during the 2-week baseline period, and 3) mood, cognitive, social, or occupational impairment due to insomnia.[22,23] Prescription and over-the-counter sleep medications were allowed provided the participant had been stabilized on the medication for at least 6 months. Pain medications were also allowed.

Individuals were excluded from participation in the parent study for the following reasons: 1) sleep disorder other than insomnia, specifically sleep apnea defined as apnea-hypopnea index greater than 15 events/h or between 10–15 events/h with an oxygen nadir below 88% or periodic limb movement

Figure 1—Study flow.



Details availablefrom the first author upon request. CBT-I = cognitive behavioral therapy for insomnia. CBT-P = cognitive behavioral therapy for pain, MRI = magnetic resonance imaging, WLC = waitlist control.

disorder defined as periodic limb movements index greater than 15 events/h; 2) bipolar disorder or seizure disorder due to potential risk of sleep restriction treatment; 3) significant medical or neurological disorder, such as cancer or dementia; 4) severe untreated psychopathology, such as schizophrenia or substance abuse; 5) cognitive impairment based on Mini-Mental State Examination[24] score below 26; and 6) concurrent participation in other nonpharmacological sleep treatment. Additionally, individuals were excluded from the neuroimaging portion of the study if they were claustrophobic, pregnant based on a urine pregnancy screen, or had implanted metal objects or electrical devices.

Study procedures were conducted at the University of Florida (UF). The UF Health Science Center Institutional Review Board (IRB-01) approved the trial protocol (No. 627-2007), and the trial was registered at https://www.clinicaltrials.gov/ under the identifier NCT02001077. All participants gave written informed consent. Participants were compensated $100 for each scanning session. They were compensated separately for participation in the parent trial at the rate of $100 for each of 3 assessment periods. They also received treatment and parking on the UF campus at no charge.

Procedures

Randomization and blinding

Following baseline assessment, participants were randomly assigned by computer-generated block randomization to 1 of 3 groups: CBT-I, CBT-P, or WLC. Participants were informed of their assignment by the project coordinator. Researchers involved in recruitment and outcome assessment were blinded to assignment, as were the statisticians who undertook the analysis. Due to the nature of the treatment, interventionist and participant blinding to assignment were not possible. Interventionists were blinded to outcome assessment.

Interventions

The CBT-I and CBT-P interventions consisted of 8 weekly 50-minute individualized sessions administered by doctoral

Table 1—Baseline demographic and clinical characteristics by treatment group.

	CBT-I	CBT-P	WLC
Age (years)	55.90 (6.52)	50.87 (14.75)	58.43 (7.44)
Education (years)	15.2 (2.78)	14.33 (1.76)	13.14 (3.02)
Female (%)	100	86.7	100
Race (%)			
Caucasian	80.0	86.7	71.4
African American	20.0	13.3	–
Native American	–	–	28.6
Ethnicity (%)			
Latino	10.0	13.3	–
Marital status, n (%)			
Married	5 (50)	7 (46.7)	5 (50)
Single	3 (30)	3 (20)	1 (20)
Cohabitating	0 (0)	1 (6.7)	0 (0)
Widowed	1 (10)	1 (6.7)	0 (20)
Divorced	1 (10)	3 (20)	1 (10)
BMI, kg/m^2	28.62 (4.72)	27.57 (3.08)	29.70 (2.40)
Insomnia duration (months)	124.00 (152.06)	146.00 (111.30)	186.00 (129.77)
Fibromyalgia duration (months)	138.14 (89.89)	79.55 (57.67)	84.00 (41.57)
Morning fatigue (minutes)	697.67 (706.45)	472.27 (624.73)	492.22 (629.26)
Morning stiffness (minutes)	534.33 (681.43)	632.27 (659.13)	551.11 (650.16)
Use of pain medications, n (%)	7 (70)	13 (86.67)	6 (85.71)
Use of sleep medications, n (%)	3 (30)	5 (33.33)	2 (28.57)

Data are presented as mean (SD) unless otherwise indicated. Participants were allowed to designate more than one race. BMI = body mass index, CBT-I = cognitive behavioral therapy for insomnia (n = 10). CBT-P = cognitive behavioral therapy for pain (n = 15), SD = standard deviation, WLC = waitlist control (n = 7).

students in the clinical psychology program at the University of Florida. Therapists received weekly and as needed supervision by a licensed clinical psychologist. Participants were given take home workbooks that contained details on treatment techniques and rationales. Full intervention details and primary sleep and pain clinical outcomes are provided elsewhere.[21] In summary, the CBT-I intervention consisted of: session 1, sleep education and sleep hygiene; session 2, stimulus control; session 3, 10-minute relaxation; session 4, sleep restriction; sessions 5 through 7, cognitive therapy; and session 8, technique review and long-term maintenance. The CBT-P intervention involved: session 1, pain education; session 2, progressive muscle relaxation; session 3, education on the activity-rest cycle, activity pacing, and autogenic relaxation; session 4, activity-rest cycle problem solving and visual imagery; sessions 5 through 7, cognitive restructuring; and session 8, technique review and long-term maintenance. The WLC completed treatment as usual and were offered either CBT-I or CBT-P treatment at no charge following study completion.

Assessments

Participants completed an experimental pain protocol during fMRI scans at baseline and then again at post-treatment. The average length of time between scans was 94.75 days (SD = 47.35; range = 70–128). Participants also completed 2 weeks of daily sleep diaries, which also included pain ratings at baseline, post-treatment, and at 6-months of follow-up as part of the parent study. Only baseline and post-treatment diary data were analyzed for the present study. Full assessment details for the parent trial are provided elsewhere.[21] Baseline and post-treatment sleep and pain outcomes for each treatment group are presented in **Table 2**. There were no significant baseline differences for any variable (all *P*s > .05). The group-by-time interaction was significant for total wake time, F (2,29) = 8.79, P = .00, η_p^2 = 0.38. All 3 treatment groups improved as indicated by decreased total wake time. The magnitude of improvement was greatest for CBT-I, t = 9.17, P < .001, Hedges g_{av} = 2.83 (large effect size), followed by CBT-P, t = 2.99, P = .01, Hedges g_{av} = .76 (moderate effect size), and then the WLC, t = 4.33, P < .001, Hedges g_{av} = 0.35 (small effect size).

Experimental pain protocol—wind-up

During each functional scan, participants completed an experimental pain protocol involving quantitative sensory testing (QST) that used thermal stimuli delivered using a 30 × 30 mm magnetic resonance imaging (MRI)–compatible contact thermode placed on the plantar surface of the right foot. The thermal stimuli were delivered using the Medoc Thermal Sensory

Table 2—Baseline and post-treatment sleep and pain outcomes by group.

Measures	CBT-I		CBT-P		WLC	
	Mean	SD	Mean	SD	Mean	SD
Total sleep time (minutes)						
Baseline	350.32	51.33	394.14	71.68	414.54	39.18
Post-treatment	405.80	58.26	423.16	105.41	417.52	57.75
Total wake time (minutes)						
Baseline	146.02	36.89	110.70	41.92	143.20	111.10
Post-treatment	49.05	24.41	77.37	40.63	102.15	94.60
Pain intensity						
Baseline	50.14	15.26	56.30	19.23	59.09	14.01
Post-treatment	42.46	18.97	47.63	24.63	68.32	16.36

CBT-I = cognitive behavioral therapy for insomnia (n = 10), CBT-P = cognitive behavioral therapy for pain (n = 15), SD = standard deviation, WLC = usual-care waitlist control (n = 7).

Analyzer (TSA-2001; Medoc Advanced Medical Systems, Ramat Yishay, Israel), which is a Peltier element–based stimulator. QST involved an initial 40-second baseline followed by 3 cycles of heat stimuli then rest. Each heat stimulus started at a baseline temperature of 41.5°C, peaked at 49.5°C, then returned to baseline for 60 seconds. The duration of each stimulus was approximately 1 second with a 3-second interstimulus interval from peak-to-peak of each stimulus in the 8-pulse train. This type of stimulus presentation results in wind-up, which is consistent with the experience of chronic pain.

Prior to each functional scan, participants reported their current pain. During the scan, participants were not asked to respond to the thermal stimuli. Immediately following each scan, participants reported their current pain level and the highest level of pain experienced during the scan. To ensure pain levels returned to prescan levels, participants reported their current level of pain every 15-seconds for the 2 minutes between functional scans.

Imaging data acquisition and preprocessing

Neuroimaging data were collected with a research-dedicated Phillips Achieva 3.0T full-body scanner and an 8-channel head coil from participants who were placed in a supine head-first position. For each participant, a high-resolution 3-dimensional anatomical image was acquired [T1-weighted, 180 sagittal slices, ACQ voxels = 1 mm^3, TR/TE (ms) = 8.1/3.7, flip angle = 8°, FOV (mm): FH, AP, RL = 240 × 240 × 180, respectively]. Following the anatomical scan, four fMRI scans were acquired using the following parameters: EPI, 38 transverse slices, slice gap (mm) = 0, ACQ voxels = 3 mm^3 voxels, TR/TE (ms) = 2000/30, flip angle 80°, FOV (mm): RL, AP, FH = 240 × 240 × 114, respectively, number of scans/volumes = 150.

The imaging data were processed using BrainVoyager (BVQX 2.8; Brain Innovation, Maastricht, The Netherlands). To reduce T1-saturation effects, 4 dummy scans were collected and discarded at the scanner prior to the actual recording and collection of the fMRI data. Image preprocessing involved 3-dimensional motion correction using sinc interpolation, slice-scan time correction with sinc interpolation, spatial smoothing with a 4-mm Gaussian kernel (full width at half maximum, FWHM), voxel-wise linear detrending, and high-pass temporal filtering to remove nonlinear drifts below 3 Hz. For each participant, the functional data were coregistered to their high-resolution 3-dimensional structural scan, which was then warped into standardized Talairach space.

Statistical analyses

To test our hypothesis, a 3 × 2 random effects (RFX) analysis of covariance was used to identify brain regions that manifested a group (CBT-I, CBT-P, WLC) × time (baseline vs post-treatment) interaction effect. This allowed us to identify cortical regions wherein wind-up, induced by the stimulus protocol, produced significantly different effects in the hemodynamic response function across the 3 groups. Potential covariates, including fibromyalgia duration, sex, and age were not significantly related to activation and were not included in the RFX-analysis of covariances. As a precaution against type-I error, a cluster was only considered significant if it met the following combined criteria: 1) the initial statistical parameter maps a *t*-value of 5, which corresponds to a *P* value ≤ .014, 2) a minimum cluster size of at least 50 contiguous voxels, and 3) the peak or most significant voxel was in a conceptually relevant area of the brain and not in white matter. The combination of these criteria established a probability of detecting a false positive among spatially correlated voxels exceeding *P* value ≤ .00002.[26] This analysis was used to identify brain regions with significant group-by-time interaction effects. The average cluster value for each person was extracted and used in the follow up analyses.

To explore specific patterns of change in activity in response to thermal pain across groups, separate repeated measures analysis of variance were conducted for each significant brain

region in the interaction to assess the effects of treatment across time. For between group comparisons, F and P values are reported (with higher F values representing less likelihood of the means being equal and $P < .05$ indicating less than 5% probability that the observation was by chance. Between group effect sizes were examined using partial eta-squared (η_p^2; 0.01 = small, 0.06 = medium, 0.14 = large).[27] Within-group effect sizes were examined using Hedges g_{av} (0.20 = small, 0.50 = moderate, 0.80 = large).[28] Anatomical coordinates of the clusters were represented in the Talairach space along the X-, Y-, and Z-axis.

RESULTS

Activation changes by group

Details about each brain region, group differences, and effect sizes as indicated by partial eta squared values are shown in **Table 3**. Twelve regions exhibited a significant group-by-time interaction. The results implicated multiple pain-related regions, including the insula and cingulate, as well as sleep-related regions, including the left middle temporal gyrus and right cingulate (see **Figure 2**). Post-hoc pairwise comparisons were also conducted for these analyses of variance to examine whether within group changes in activation were statistically significant (see last column in **Table 3**). The CBT-I group demonstrated significantly lower activation in response to wind-up stimuli following treatment in 8 brain regions, including the right insula, right inferior frontal gyrus, right middle occipital gyrus, right superior temporal gyrus, right lentiform nucleus, right cingulate gyrus, left inferior occipital gyrus, and left inferior frontal gyrus. The effect sizes were large and ranged from 0.82 to 1.18. The CBT-P group demonstrated significantly lower activation response to wind-up stimuli in the following 3 regions: right cingulate gyrus, left inferior occipital gyrus, left inferior frontal gyrus. The effect sizes were moderate to large and ranged from 0.66 to 0.82. CBT-P also demonstrated significantly higher activation in the following 3 regions: left angular gyrus, left superior temporal gyrus, and left middle frontal gyrus. The effect sizes were moderate to large and ranged from 0.59 to 1.02. In contrast, the WLC group demonstrated significantly higher activation in response to wind-up stimuli in the following 6 regions at post-treatment: right inferior frontal gyrus, right lentiform nucleus, left angular gyrus, left superior temporal gyrus, left middle frontal gyrus, and left middle temporal gyrus. The effect sizes were large and ranged from 0.80 to 3.47. **Figure 3** illustrates the overall pattern of results. The CBT-I group showed significantly lower activation in response to wind-up stimuli following treatment, while the control group showed higher activation in response to wind-up stimuli. The CBT-P group falling somewhere in between with significantly lower activation in some regions and higher activation in others. Interestingly, for the 3 regions for which both treatments demonstrated lower activation in response to wind-up stimuli, the magnitude of the decrease was greater for the CBT-I group than for the CBT-P group.

Based on the observed pattern of change across groups, the next analyses examined how behavioral changes observed following treatment were related to changes in brain activation in response to pain following treatment. Separate linear regression analyses were conducted for each region to examine whether changes in average sleep and pain intensity from baseline to post-treatment predicted changes in activation. For these analyses, we utilized sleep diaries to assess behavioral sleep parameters and ratings of pain intensity, as these measures parallel each other in patient self reports and have the greatest clinical relevance. Residualized change scores were entered into the regressions, with total sleep time (TST; total minutes asleep), total wake time (TWT; total minutes of wake time during the night), and ratings of pain intensity as predictors.

Change in pain intensity did not significantly predict changes in activation in response to wind-up stimuli in any region and was subsequently dropped from the models. The regressions revealed that improved sleep predicted a decrease in activation in response to wind-up stimuli in 7 regions. As shown in **Table 4**, the results revealed that decreased TWT predicted decreased activation in response to pain in the right superior temporal gyrus and right middle occipital gyrus. The increase in TST predicted decreased activation in the left angular gyrus, left superior temporal gyrus, left middle frontal gyrus, and left middle temporal gyrus. Decreased TWT trended toward predicting decreased activation in response to pain in the left angular gyrus. Both decreased TWT and increased TST trended toward predicting decreased activation in response to pain in the left inferior occipital gyrus.

Additional regression analyses controlling for sleep and pain medication use showed they had negligible impact on changes in brain activation in response to pain. Sleep medication use was not a significant predictor for any region, while pain medication use was only significant for a single region (right middle occipital gyrus, $R^2 = 0.53$, $F = 10.41$, $P < .001$; pain medication use $B = 0.403$, SE = 0.110, b = 0.50, $t = 3.67$, $P < .001$; TWT $B = 0.003$, SE = 0.001, b = 0.37, $t = 2.69$, $P = .01$; TST $B = –0.001$, SE = 0.001, b = –0.15, $t = –.98$, $P = .34$).

Exploratory analyses

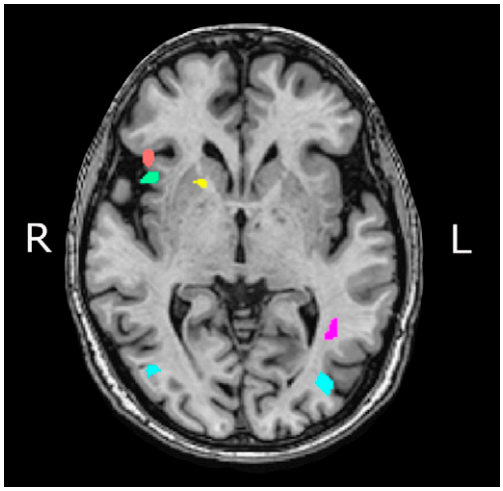
As reported previously,[21] we did not find any improvement in polysomnographically (PSG) assessed sleep variables following CBT-I, CBT-P, or WLC. However, given the present results showing associations between behavioral sleep variable improvement (TST/TWT) and pain reduction across treatment groups, we were interested in exploring whether treatment-related change in pain were also associated with changes in sleep architecture variables (%stage 1,) obtained through PSG assessment. For full details on PSG methods, see McCrae et al, 2019[21]. Briefly, at baseline and post-treatment, PSG outcomes were obtained via a 25-channel AURA Portable Recording System (Grass Technologies, West Warwick, RI). Consistent with ambulatory polysomnography recommendations, monitoring consisted of 10 electroencephalography measures (F2, C2, O2, ground, reference, M1, M2), 2 electro-oculography, and 3 chin electromyography according to standard placements, respiratory inductance plethysmography assessing thoracic and abdominal effort, oximeter assessing pulse and oxygen saturation, electrocardiogram, right and left anterior tibialis electromyography, oral-nasal airflow thermocouple, and nasal cannula pressure transducer.[29–31] The PSG studies were

Table 3—Brain regions showing significant interactions ($P < .05$) for brain activation in response to thermal stimuli.

Region	Group-Level Analysis					Post-hoc Analysis: Within-Group Change	
	F	*P*	η_p^2	Size	X,Y,Z	Group	*t*, *P*, Hedges g_{av}
Right hemisphere							
Insula	5.67	.008	.28	275	38, 16, 0	*CBT-I	5.43, .00, 1.18
						CBT-P	–0.83, .42, 0.26
						WLC	0.78, .47, 0.43
Inferior frontal gyrus	10.26	.000	.41	234	41, 25, 0	*CBT-I	3.88, .00, 1.06
						CBT-P	–0.73, .48, 0.20
						*WLC	–4.20, .01, 1.73
Middle occipital gyrus	6.81	.004	.32	268	38, –74, 3	*CBT-I	2.78, .02, 0.83
						CBT-P	–1.40, .18, 0.33
						WLC	–1.41, .21, 0.48
Superior temporal gyrus	11.59	.000	.44	204	32, 4, –15	*CBT-I	4.50, .00, 0.96
						CBT-P	–1.50, .16, 0.25
						WLC	0.19, .86, 0.10
Lentiform nucleus (Putamen)	17.36	.000	.55	316	17, 10, –3	*CBT-I	6.73, .00, 1.40
						CBT-P	–0.39, .70, 0.10
						*WLC	–2.74, .03, 0.86
Cingulate gyrus	10.61	.000	.42	262	17, –14, 42	*CBT-I	3.78, .00, 0.82
						*CBT-P	2.98, .01, 0.66
						WLC	1.24, .26, 0.61
Left hemisphere							
Angular gyrus	17.91	.000	.55	317	–26, –55, 34	CBT-I	2.20, .06, 0.57
						*CBT-P	–2.80, .01, 0.59
						*WLC	–2.72, .03, 1.76
Superior temporal gyrus	28.89	.000	.67	1312	–37, –47, 18	CBT-I	0.91, .39, 0.28
						*CBT-P	–3.61, .00, 0.83
						*WLC	–2.94, .02, 0.80
Middle frontal gyrus	12.77	.000	.47	227	–37, 25, 40	CBT-I	1.93, .09, 0.66
						*CBT-P	–3.68, .00, 1.02
						*WLC	–4.55, .00, 1.20
Inferior occipital gyrus	7.51	.002	.34	698	–34, –77, 0	*CBT-I	3.05, .01, 0.97
						*CBT-P	3.05, .01, 0.80
						WLC	–0.31, .77, 0.14
Middle temporal gyrus	10.17	.000	.41	356	–41, –56, 0	CBT-I	1.00, .34, 0.29
						CBT-P	–1.89, .08, 0.38
						*WLC	–8.77, .00, 3.47
Inferior frontal gyrus	9.27	.001	.39	160	–43, 16, 12	*CBT-I	3.36, .01, 0.98
						*CBT-P	2.43, .03, 0.82
						WLC	–1.42, .20, 0.30

*Significant within-group change ($P < .05$). *F* represents *F* value of repeated measures analysis of variance at the group level and *P*, the corresponding *P* value. η_p^2 represents partial eta-squared effect size. Post-hoc analyses were carried out in regions that showed a significant difference at the group level (rightmost column). Results are reported as *t* value, *P* value, and effect size represented by Hedges g_{av}. η_p^2 .14 = large. Size = number of contiguous voxels. X, Y, Z represent the anatomical location of the cluster along X-, Y-, and Z-axes in Talairach space. Hedges g_{av} 0.20 = small, 0.50 = moderate, 0.80 = large. CBT-I = cognitive behavioral therapy for insomnia, CBT-*P* = cognitive behavioral therapy for pain, WLC = usual-care waitlist control.

Figure 2—Regions showing significant group-by-time interactions in pain-related brain activity.



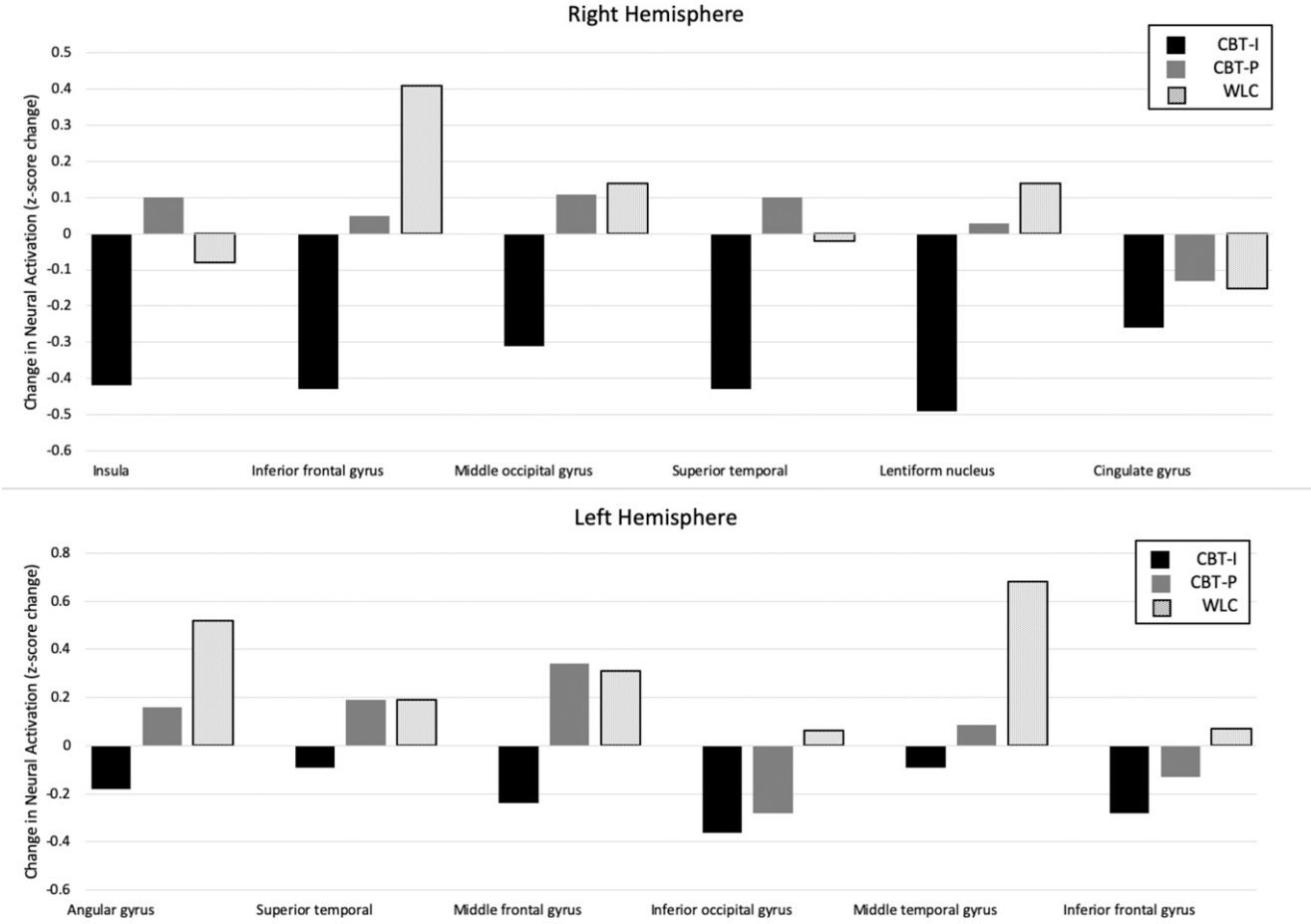
scored following the criteria used by the Sleep Heart Health Study[20] by a registered polysomnographic technologist blinded to group assignment.[31] Random effects analysis of covariance identified regions with significant group-by-time interactions in brain activation in response to pain. Linear regressions using residualized change scores were conducted for each significant region to examine how pain and PSG sleep changes in % stages 1–3 non–rapid eye movement (non-REM), and % REM were related to brain activation changes.

Regression results showed that %stage 2 and %REM sleep were not significantly associated with change in activation in any region and were dropped from regression models. As shown in **Table 5**, increased %stage 1 and %stage 3 predicted decreased brain activation in response to pain in 7 of the 12 regions (*P*s < .01), accounting for 19%–45% of the variance.

DISCUSSION

Prior studies showed that fibromyalgia is associated with greater activation in brain regions associated with pain processing.[7]

Figure 3—Changes in pain-related brain activity for regions with significant group-by-time interactions.



Positive values indicate increased pain-related activity and negative values indicate decreased pain-related activity. CBT-I = cognitive behavioral therapy for insomnia, CBT-P = cognitive behavioral therapy for pain, WLC = waitlist control.

Table 4—Multiple regression results of changes in total wake time and total sleep time predicting neural activation changes in response to experimental pain (n = 32).

Region	R^2	*F*	*P*	*B*	SE	*β*	*t*	*P*
R. Insula	.03	0.49	.62					
TWT				.001	.002	–.10	0.76	.45
TST				.000	.001	.14	–0.55	.59
R. Inferior frontal gyrus	.17	2.88	.07†					
TWT				.002	.001	.28	1.62	.12
TST				–001	.001	–.27	–1.59	.12
R. Superior temporal gyrus	.18	3.25	.05*					
TWT				.004	.001	.43	2.54	.02*
TST				.000	.001	.00	–0.00	.99
R. Middle occipital gyrus	.30	6.22	.006*					
TWT				.004	.001	.51	3.27	.003*
TST				–.001	.001	–.15	–0.98	.34
R. Lentiform nucleus	.08	1.22	.31					
TWT				.002	.001	.28	1.56	.13
TST				.000	.001	.06	0.32	.75
R. Cingulate gyrus	.17	2.94	.07†					
TWT				.002	.001	.34	1.99	.06†
TST				–.001	.001	–.27	–1.58	.125
L. Angular gyrus	.47	12.66	.00*					
TWT				.002	.001	.26	1.87	.07†
TST				–.003	.001	–.66	–4.84	.00*
L. Superior temporal gyrus	.41	10.16	.00*					
TWT				–.001	.001	–.16	–1.12	.27
TST				–.003	.001	–.64	–4.46	.00*
L. Middle frontal gyrus	.21	3.92	.03*					
TWT				.002	.001	.20	1.23	.23
TST				–.002	.001	–.39	–2.38	.02*
L. Inferior occipital gyrus	.21	3.92	.03*					
TWT				.004	.002	.30	1.83	.08†
TST				–.002	.001	–.32	–1.92	.07†
L. Middle temporal gyrus	.23	4.25	.02*					
TWT				.000	.001	.013	0.08	.94
TST				–.002	.001	–.48	–2.89	.007*
L. Inferior frontal gyrus	.07	1.02	.37					
TWT				.002	.001	.25	1.38	.18
TST				.000	.001	.095	0.52	.60

*P < .05, †P < .10. Change in pain intensity is not included in the models shown, because it was not significantly correlated with changes in neural activation and did not improve the fit of the regression models or significantly predict change in neural activation in any region. L = left, R = right, TST = total sleep time, TWT = total wake time.

Preliminary results from the present pilot study suggest that 8 weeks of CBT-I prompted greater decreases in activation in response to pain, using a wind-up protocol as an experimental proxy for central sensitization, across more regions than CBT-P. Additionally, CBT-P increased activation in response to pain in some areas, while the waitlist increased it in multiple areas. The overall pattern of neural activation changes suggests CBT-I may lead to a reversal of the greater activation observed in response to pain in fibromyalgia. In other words, CBT-I holds promise for reversing central sensitization in patients with fibromyalgia.

Both CBT-I and CBT-P resulted in lower functional activation in response to pain following treatment. However,

consistent with our hypothesis, participants who underwent CBT-I showed even lower functional activation in response to pain across a greater number of brain regions following treatment compared to CBT-P, which also showed increased functional activation in some areas. For example, the insula, claustrum, and cingulate are well known pain[32]- and sleep[33]-related brain regions (eg, inferior frontal and occipital cortices). These functional findings provide novel preliminary evidence that both pain- and nonpain-related processes may contribute to and help maintain central sensitization. They also demonstrate that CBT-I, a treatment for insomnia, may prompt a decrease in central sensitization, while CBT-P's impact is unclear as it prompted decreased activation in some regions and increased activation in others. It is likely that the mechanism by which CBT-I prompts these neural changes is a reduction in chronic arousal specifically related to insomnia rather than pain.[34] Unlike CBT-P, the CBT-I implemented in the present study specifically targeted physiological and cognitive arousal related to poor sleep through relaxation and cognitive restructuring techniques, respectively.[21] Although CBT-P includes relaxation and cognitive restructuring, these are provided within the context of pain symptoms, not sleep. Thus, the functional changes observed here may be more closely linked to sleep-related mechanisms and associated symptoms. Results suggest that improving sleep perceptions are a plausible candidate for explaining the relationships of cognitive states, including catastrophizing and somatic focus, and ongoing nociceptive input[35] to central sensitization and chronic pain. More specifically, self-reported health complaints, such as insomnia complaints and associated arousal, may contribute to critical changes to hypothalamic-pituitary-adrenal and central nervous system functioning that prompt increased sensitivity to stimulation, particularly pain.[15,16] We propose CBT-I improves neural pain processing by improving sleep and reducing arousal, thereby reversing the negative hypothalamic-pituitary-adrenal and central nervous system changes that sustain chronic pain. In other words, we propose CBT-I reverses central sensitization.

Interestingly, our post-hoc regression analyses revealed potential sleep mechanisms, as measured by both self-reported behavioral sleep and objective sleep architecture measures, that underlie the observed improvement in the brain's response to pain following CBT-I. As previously reported,[21] although CBT-P also improved self-reported wake time after sleep onset, sleep efficiency, and sleep quality at post-treatment, effect sizes were larger for CBT-I. Therefore, the consistent pattern of activation changes reported here for CBT-I but not CBT-P may indicate that a higher threshold of perceived sleep improvement is required to elicit functional neural plasticity consistent with the reduction of central sensitization. Specifically, regression results suggest that it is improvements in self-reported TWT and TST, as well as increased percentages of lighter stage 1 and deeper stage 3 sleep, that may underlie these functional changes in the brain's response to thermal pain following CBT-I (see **Table 4** and **Table 5**). Importantly, findings for PSG-assessed variables suggest that changes in non-REM sleep architecture likely additionally contribute to or are mechanisms through which behavioral self-reported sleep variables contribute to the TST-related associations with activation changes, consistent with reduction or reversal in central sensitization. Given that greater time spent awake during the night is associated with increased cognitive and physiological arousal as well as increased activity in brain regions associated with sleep-wake,[36] it will be important for future research to also examine whether the activation changes are specific to reductions in chronic arousal related to insomnia, targeted by CBT-I. For example, future work should examine additional measures of cognitive (eg, perceived stress) and physiological arousal (eg, heart rate variability and/or cortical metabolism) in order to more comprehensively evaluate mechanisms underlying activation changes following CBT-I. Additionally, although we did not observe treatment-related changes in TST in the prior main clinical outcomes article,[21] the present results suggest that in addition to TWT, TST may have also played a role in reducing neural activation in response to pain. Taken together, the present pilot results suggest that both self-reported and objective sleep mechanisms play an important role in neural pain processing and central sensitization. These preliminary results support targeting sleep as a mechanism for improving neural pain processing in adults with fibromyalgia and insomnia.

The present pilot study did not examine long term effects of treatment on fMRI results as it was supported by a supplemental award that provided funding for baseline and post-treatment neuroimaging data collection only. Thus, an important question for future research is whether the decreased activation in response to pain observed immediately following CBT-I would have been maintained or possibly enhanced at follow-up. This is a main objective of our currently in progress SPIN II randomized controlled trial (NCT03744156) examining the impact of CBT-I, compared to an active sleep hygiene education control, on neural activation in response to pain up to 12 months following treatment in the full trial sample. Furthermore, closer examination of the effect sizes of the previously reported[21] self-reported sleep outcomes at 6-month follow-up provides reason to speculate that given more time, CBT-P may also have decreased activation in response to pain (indicative of improved central sensitization) at follow-up. For instance, by 6 months, the magnitude of improvement for CBT-P on sleep outcomes more closely matched the levels of moderate to large improvement obtained by CBT-I. Therefore, based on these findings, another important question for future research is whether CBT-P's increased impact on sleep at follow-up indicates it might also reduce central sensitization if given sufficient time. Changes in brain function are not necessarily associated with magnetic resonance–detectable changes in structure. However, when the present findings are compared to previously reported findings regarding CBT-I-related structural neural plasticity in sleep/pain-related cortical regions,[25] the cumulative findings suggest structural recovery in CBT-I may also be associated with reductions in functional activation during heat stimulation in inferior frontal lobe structures. Considered within the context of previously reported clinical sleep and pain outcomes,[21] the findings are consistent with our hypothesis that improvements in sleep will lead to reduction or even reversal in central sensitization and clinical pain. They also prompt speculation about the importance of the temporal relationships among these variables.

Table 5—Multiple regression results of changes in % stage 1 and % stage 3 predicting neural activation changes in response to experimental pain (n = 32).

Region	R^2	*F*	*P*	*B*	SE	β	*t*	*P*
R. Inferior frontal gyrus	.20	3.89	.001*					
% Stage 1				.000	.001	.08	0.59	.82
% Stage 3				.002	.001	.45	1.62	.006*
R. Superior temporal gyrus	.19	3.52	.05*					
% Stage 1				.004	.001	.43	2.54	.02*
% Stage 3				.000	.001	.00	–0.00	.99
R. Middle occipital gyrus	.33	6.47	.004*					
% Stage 1				–.001	.001	–.15	–0.98	.34
% Stage 3				.004	.001	.51	3.27	.003*
L. Angular gyrus	.45	13.67	.00*					
% Stage 1				.002	.001	.26	1.87	.07†
% Stage 3				–.003	.001	–.66	–4.84	.00*
L. Superior temporal gyrus	.43	11.16	.00*					
% Stage 1				–.001	.001	–.16	–1.12	.27
% Stage 3				–.003	.001	–.64	–4.46	.00*
L. Middle frontal gyrus	.27	4.96	.02*					
% Stage 1				.002	.001	.20	1.23	.23
% Stage 3				–.002	.001	–.39	–2.38	.02*
L. Inferior occipital gyrus	.23	4.28	.04*					
% Stage 1				.004	.002	.30	1.83	.06†
% Stage 3				–.002	.001	–.32	–1.92	.08†
L. Middle temporal gyrus	.45	13.67	.00*					
% Stage 1				.000	.001	.013	0.08	.94
% Stage 3				–.002	.001	–.48	–3.17	.007*

*$P < .05$, †$P < .10$. Change in pain intensity is not included in the models shown, because it was not significantly correlated with changes in neural activation and did not improve the fit of the regression models or significantly predict change in neural activation in any region. L = left, R = right.

The present pilot study has several limitations. First, the small sample size in each treatment group limits generalizability of results. Importantly, however, we present novel promising preliminary evidence suggesting how CBT-I may impact neural response to pain, and potentially reverse central sensitization in patients with fibromyalgia and insomnia. Future studies with larger sample sizes are needed to further explore these findings. Second, as previously mentioned, the lack of long-term imaging follow-up precludes conclusions regarding whether functional neural changes seen in CBT-I were maintained over time. As noted above, our currently in progress SPIN II trial addresses the sample size and longitudinal efficacy limitations of this pilot study. Third, it is unknown whether CBT-P may have impacted functional activation over a longer period, similar to the pattern observed in behavioral sleep measures. Fourth, the SPIN trial did not study cognitive and physiological arousal—key mediators according to our conceptual model—the cognitive activation theory of stress, or physiological sleep. Finally, our sample consisted primarily of middle-aged women, all of whom had comorbid fibromyalgia and insomnia. While this preponderance of middle-aged women is representative of patients with fibromyalgia,[37] it is unclear whether our findings are more broadly generalizable to men with fibromyalgia, patients with fibromyalgia with subclinical insomnia or without insomnia, and individuals of both sexes with other chronic pain conditions.

In conclusion, this pilot study shows functional activation in response to experimental pain decreased following CBT-I across multiple brain regions associated with pain and sleep processing. These findings provide preliminary support for our hypothesis that improving sleep would reduce or ideally reverse central sensitization. Findings support the link between sleep and pain neural mechanisms and suggest that behavioral treatment targeting insomnia symptoms and maladaptive sleep behavior may prompt functional neural plasticity.

ABBREVIATIONS

CBT-I, cognitive behavioral therapy for insomnia
CBT-P, cognitive behavioral therapy for pain

fMRI, functional magnetic resonance imaging
PSG, polysomnograph, -y, -ical, -ically
REM, rapid eye movement
TST, total sleep time
TWT, total wake time
WLC, wait-list control

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