Research Paper

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Enhanced mindfulness-based stress reduction in episodic migraine: a randomized clinical trial with magnetic resonance imaging outcomes

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Abstract

We aimed to evaluate the efficacy of an enhanced mindfulness-based stress reduction (MBSR+) vs stress management for headache (SMH). We performed a randomized, assessor-blind, clinical trial of 98 adults with episodic migraine recruited at a single academic center comparing MBSR+ (n = 50) with SMH (n = 48). MBSR+ and SMH were delivered weekly by group for 8 weeks, then biweekly for another 8 weeks. The primary clinical outcome was reduction in headache days from baseline to 20 weeks. Magnetic resonance imaging (MRI) outcomes included activity of left dorsolateral prefrontal cortex (DLPFC) and cognitive task network during cognitive challenge, resting state connectivity of right dorsal anterior insula to DLPFC and cognitive task network, and gray matter volume of DLPFC, dorsal anterior insula, and anterior midcingulate. Secondary outcomes were headache-related disability, pain severity, response to treatment, migraine days, and MRI whole-brain analyses. Reduction in headache days from baseline to 20 weeks was greater for MBSR+ (7.8 [95% CI, 6.9-8.8] to 4.6 [95% CI, 3.7-5.6]) than for SMH (7.7 [95% CI 6.7-8.7] to 6.0 [95% CI, 4.9-7.0]) (*P* = 0.04). Fifty-two percent of the MBSR+ group showed a response to treatment (50% reduction in headache days) compared with 23% in the SMH group (*P* = 0.004). Reduction in headache-related disability was greater for MBSR+ (59.6 [95% CI, 57.9-61.3] to 54.6 [95% CI, 52.9-56.4]) than SMH (59.6 [95% CI, 57.7-61.5] to 57.5 [95% CI, 55.5-59.4]) (*P* = 0.02). There were no differences in clinical outcomes at 52 weeks or MRI outcomes at 20 weeks, although changes related to cognitive networks with MBSR+ were observed. Enhanced mindfulness-based stress reduction is an effective treatment option for episodic migraine.

Keywords: Headache, fMRI, Brain, Intervention, Nonpharmacological, Treatment

1. Introduction

Migraine is a severe and often disabling neurological disorder,[30,44] and standard preventative agents frequently create challenging side effects.[49,57] Migraine guidelines[51] include nonpharmacological preventative treatments, and mindfulness-based stress reduction (MBSR) recently has been shown to improve pain and functional outcomes in chronic low back pain.[18] Yet meditation and mindfulness therapies show only modest benefits to date in reducing the frequency of migraine.[3,34,75] The outcomes of MBSR in reducing pain[32] and migraine frequency[3] may improve if training is enhanced to include a longer period of learning because greater home practice yields better outcomes in MBSR.[50] Because medication can contribute to the frequency of headache,[13] MBSR may be an effective nonpharmacological prevention strategy that has become widely available throughout the United States and Europe in recent years.

Migraine headaches are due to acute alterations in the trigeminovascular system, and changes in brain perfusion include widespread increases and decreases in brain activity.[12,17,20] Beyond the changes known to occur during attacks, mild cognitive deficits occur between attacks[70,74] and brain structure is altered relative to controls.[7,39] These brain changes involve cognitive and emotional circuits,[19] particulary the insula,[10] left dorsolateral prefrontal cortex (DLPFC), and anterior/midcingulate cortex (ACC/MCC).[48] Our previous work on pain and cognition has focused on the role of the DLPFC and the cognitive task network known as the extrinsic mode network (EMN)—which is a brain network activated across multiple types of cognitive challenges (eg, conflict and working memory) and anticorrelated with the default mode network[38]—and the connectivity of these regions to the anterior insula.[15,58,60,61,63,65] The demands of recurring pain deplete cognitive and emotional resources,[58] and

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treatments that increase the efficiency of information processing, or cognitive efficiency, may be particularly beneficial for painful conditions such as migraine. Although mindfulness meditation can reduce acute pain through complex cortical and thalamic mechanisms that are independent of endogenous opioids,[79–83] long-term practice seems to increase cognitive efficiency. Long-term meditation practitioners show structural changes in brain areas involved in cognitive and emotional processing (insula, ACC/MCC, and prefrontal cortex[27]), and mindfulness training changes brain function in these and other areas, with consistent long-term changes in insula cortex.[31,78] The focused attention involved in mindfulness activates these cognitive networks,[21] and even brief mindfulness training improves cognitive efficiency and increases engagement of left DLPFC.[2] Increased cognitive efficiency contributes to control over pain in long-term mindfulness practitioners.[33]

This trial compared enhanced MBSR (MBSR+) with an active control on clinical and imaging outcomes in episodic migraine. We hypothesized that MBSR+ would reduce headache frequency (primary) and reduce migraine-related disability (secondary). We also hypothesized that MBSR+ would alter the structure and function of brain areas and networks involved in cognitive efficiency, including increased gray matter volume in the DLPFC, MCC, and insula; decreased activation of left DLPFC and EMN during cognitive challenge; and reduced resting state connectivity from anterior insula to left DLPFC and cognitive task network.

2. Methods

The study protocol was approved by the Johns Hopkins School of Medicine and the University of Maryland Baltimore Institutional Review Boards. Participants were recruited from local headache clinics, primary care providers, and the community in 8 cohorts (9-18 participants/cohort) from June 2014 to February 2017. Cohorts included participants randomized to stress management for headache (SMH) or MBSR+, with both study arms running concurrently. Recruited individuals were 18 to 65 years of age and met International Classification of Headache Disorders criteria for migraine with or without aura.[37] Eligibility was assessed first by telephone (**Fig. 1**), then a screening visit. After written informed consent, screening established ≥1 year history of a migraine diagnosis and excluded individuals who reported severe or unstable psychiatric symptoms, used opioid medications, had previous experience with mindfulness or concurrent treatment expected to affect mindfulness/stress reduction (see Protocol for full inclusion/exclusion). Potential participants completed at least 28 days of an electronic daily diary to establish eligibility (4-14 headache days in 28 days), which served as the baseline measure of headache frequency. Eligible subjects then attended the magnetic resonance imaging (MRI) session, including written informed consent, questionnaires, and quantitative sensory testing.

2.1. Assessments

Study questionnaires were completed online at baseline, week 10 (after 8 weeks of MBSR+/SMH), week 20 (after completion of MBSR+/SMH), and at week 52. Magnetic resonance imaging visits at baseline, week 10, and week 20 were conducted by staff masked to treatment group. All MRI scans used a Siemens TimTrio 3T MRI scanner with a 32-channel head coil through March 2017, then a Siemens 3T Prisma Fit MRI scanner with a 64-channel head coil (see below for details). Scans included a T1 high-resolution anatomical scan, a resting state functional MRI (fMRI) scan, and fMRI scans during completion of 2 runs of painful thermal stimulation and 2 runs of cognitive challenge (the multisource interference task [MSIT]).[14]

2.2. Randomization

Randomization (1:1) was stratified by the presence/absence of another chronic pain disorder and headache frequency from the baseline headache diary (low: 4-8; high: 9-14 headache days per 28 days). The randomization schedule was generated online (randomization.com) and stored in a locked cabinet by nonstudy staff. Assignment occurred by nonstudy staff when the participant arrived for the first day of class. Thus, intervention staff were blinded to assignment until the first day of class. Participants were instructed not to discuss their assignment with assessors, who were blinded to assignment. The principal investigator and statistician remained blinded until completion of the study and analysis.

2.3. Interventions

Participants were instructed to continue stable use of prescribed preventative treatments and continue use of acute abortives as needed. Separate groups for each intervention met for about 2 hours weekly for 8 weeks then biweekly for another 8 weeks. A trained expert in the content for each intervention used a manualized protocol that included participant handouts and materials for home use. MBSR+ was administered by 2 experienced, certified instructors (10 and 40 years of meditation experience). Stress management for headache was delivered by a nurse practitioner (11-year experience treating headache patients). Checklists were completed by instructors at the end of sessions to verify all components were delivered. Missed sessions were made up individually in person or by phone.

The enhanced MBSR (MBSR+) included 12 sessions over 4 months, including 8 weekly sessions followed by 4 biweekly sessions. The first 8 sessions adapted the MBSR program developed by Kabat-Zinn[40] to include trauma-informed methods of teaching and emphasized loving kindness to distress.[42] Study participants were provided with audio CDs and handouts and a personal copy of *Full Catastrophe Living* by Jon Kabat-Zinn. Each session included a longer arriving practice, and a loving kindness meditation was included at week 2 and, at the retreat, held between weeks 6 and 8. The week 8 class was adapted to focus on applying learning to migraines before, during, and after an attack and engaging participants in deciding, which MBSR practices they wished to increase practice of during the second 8 weeks of the MBSR+ program. The additional 4 biweekly sessions enhanced typical MBSR training by encouraging continued mindfulness practice and self-compassion and emphasizing sympathetic joy, equanimity, and gratitude. The format of these biweekly sessions was similar to the original program and included both didactic content and mindfulness practice, including body scan, yoga, sitting, and walking meditations.

Stress management for headache included 12 sessions over 4 months focused on didactic content about the role of stress and other triggers in headaches and followed a similar format and timing to the MBSR+ sessions, minus the retreat. Topics included stress at work and home; coping with stress mental health and personality; sleep hygiene; pain education; and medications for migraine. Information, group discussion, and social support among group members were emphasized; behavior change and specific skill development were not addressed. Each session included a 10-minute period of standardized muscle stretching exercises. In addition to educational handouts, participants were provided with a personal copy of *The Migraine Brain* by Carolyn Bernstein.

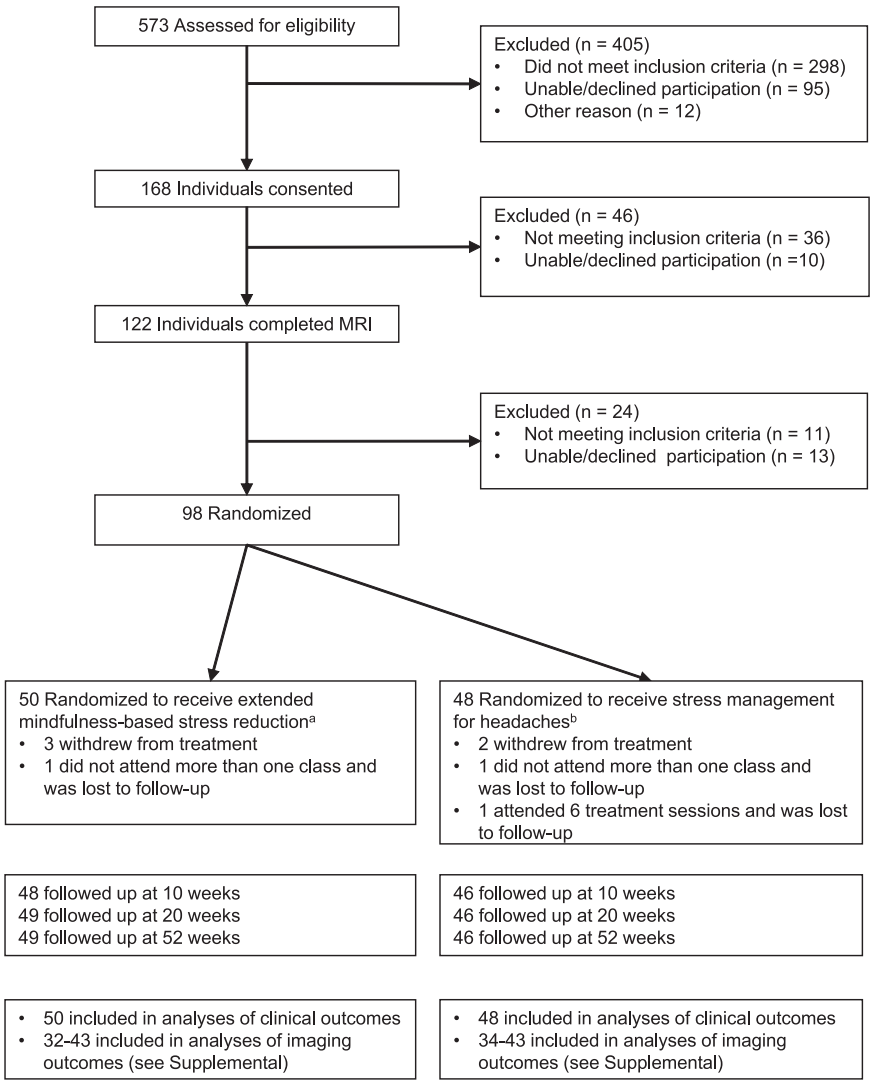

Figure 1. Participant flow through trial comparing extended mindfulness-based stress reduction and stress management for migraine headache. [a]Of the 50 participants randomized to receive enhanced mindfulness-based stress reduction, 43 completed all 12 sessions. Participants were recruited in 8 separate cohorts (range of 4-8/cohort). [b]Of the 48 participants randomized to receive stress management for headaches, 40 completed all 12 sessions. Participants were recruited in 8 separate cohorts (range of 2-11/cohort).

2.4. Measures

Sociodemographic and medical data were obtained at baseline (**Table 1**). Clinical and imaging outcome measures were collected at baseline, at week 10 after the first phase of MBSR+/SMH (secondary), and week 20 after the second phase of MBSR+/SMH (primary), and clinical outcome measures were also collected at week 52 (secondary). The week 20 timepoint, along with the 28-day period of prospective diaries that patients completed, conforms to current guidelines on randomized controlled trials (RCTs) for migraine prophylaxis.[68]

2.5. Primary outcomes

2.5.1. Clinical outcomes

The primary outcome was measured as the change from baseline to week 20. Headache frequency was measured using an electronic daily diary for 28 days based on the National Institute of Neurological Disorders and Stroke preventive therapy headache diary, which was provided through an email link. When fewer than the full 28 days were completed, the proportion of headache days was calculated (number of headache days/total number of diary days) and then multiplied by 28 to get a continuous variable for headache days. Note: in the clinical trial registration, we included headache-related disability as a primary outcome. However, given previous migraine RCTs have almost exclusively used headache frequency as the primary outcome, we chose to limit focus on that sole primary outcome.

2.5.2. Imaging outcomes

Brain function was measured as activation during cognitive task[14] performance in left DLPFC and cognitive task network (EMN), and resting state connectivity of right dorsal anterior insula (daINS) to left DLPFC and cognitive task network (EMN). Brain structure was measured as gray matter volume (GMV) in DLPFC, cingulate, and anterior insula. Regions of interest (ROIs) were defined from the cognitive task group activation map for all participants combined at baseline. Peak voxels for each region were selected, a 4-mm radius sphere was created, and data were extracted from the

Table 1

Sample characteristics.

Characteristic	All, n = 98	Randomized to SMH, n = 48	Randomized to MBSR+, n = 50	*P*
Age: median years (range)	36 (18-65)	36 (21-63)	36 (18-65)	NS
Gender				NS
M	9 (9.2)	6 (12.5)	3 (6.0)	
F	89 (90.8)	42 (87.5)	47 (94.0)	
Race				NS
White	71 (72.4)	36 (75.0)	35 (70.0)	
African American	17 (17.3)	7 (14.6)	10 (20.0)	
Other	9 (9.1)	5 (10.4)	4 (8.0)	
Presence of idiopathic pain				NS
No	70 (71.4)	35 (72.9)	35 (70.0)	
Yes	28 (28.6)	13 (27.1)	15 (30.0)	
Headache frequency				NS
Low (4-8)	50 (51.0)	25 (52.1)	25 (50.0)	
High (>8 and <15)	48 (49.0)	23 (47.9)	25 (50.0)	
Education				$P = 0.21$
Up to some college	20 (20.4)	7 (14.6)	13 (26.0)	
College or more	78 (79.6)	41 (85.4)	37 (74.0)	
Medication/vitamin, any				$P = 0.09$
No	83 (90.8)	44 (91.7)	39 (78.0)	
Yes	15 (9.2)	4 (8.3)	11 (22.0)	
Median days (range) between MRI and first intervention.		10 (0-21)	10 (1-25)	NS

N (%) unless otherwise stated.
MBSR, mindfulness-based stress reduction; MRI, magnetic resonance imaging; SMH, stress management for headache.

scan of interest for each subject. Further details on neuroimaging data and analysis are provided below.

2.6. Secondary outcomes

2.6.1. Clinical outcomes

Secondary outcomes were assessed at weeks 10, 20, and 52. Headache-related disability was measured using the 6-item Headache Impact Test[43] that shows strong psychometric properties.[77] Headache intensity was computed as the average of all headache intensity ratings from the electronic daily diary.[68] Response to treatment was defined as ≥50% reduction in number of headache days[68] from baseline to week 20. A migraine[14] day was coded when at least 2 of the following criteria were met: unilateral, pulsating, moderate/severe pain, aggravated by routine activity; and at least one of the following criteria were met: nausea/vomiting or light/noise sensitivity.

2.6.2. Imaging outcomes

Whole-brain analyses of gray matter volume, activation to pain, activation to cognitive challenge, and resting state connectivity of the insula cortex were measured using Sandwich estimator toolbox[35] (see below).

2.7. Sample size

Using a 0.050 two-sided significance level, a sample of 90 subjects randomized to 2 treatment groups (1:1) provides 80% power to detect an effect size (Cohen's d) of at least 0.60 in change of headache frequency for MBSR+ relative to SMH using a *t* test and the difference between a proportion of responders for MBSR of 0.435 (20/45) and for SMH of 0.150 (7/45) using a Fisher's exact test.

2.8. Subjects included in imaging analyses

Magnetic resonance imaging analyses were per protocol. Subjects were excluded from imaging for the following reasons, for each scan type: missing data from baseline; if baseline data are available, missing data from weeks 10 and 20; excessive motion; abnormal anatomy; technical issue (most commonly Medoc Pathway failure); claustrophobia or inability to tolerate thermal stimulation; discontinued treatment; and refused MRI (at a follow-up visit).

A total of 8 subjects were removed from all MRI analyses because they had useable data for only one or no scan sessions, and 2 others were removed because they did not complete treatment. An additional subject was excluded because of a frontal lobe encephalomalacia due to olfactory meningioma removal (late disclosure). Two other subjects were excluded from fMRI analyses only, one who had very high motion and one had no useable functional data. See Supplementary Table 1 for subjects included in each analysis (available at http://links.lww.com/PAIN/A979).

2.9. Magnetic resonance imaging data acquisition

T1 MPRAGE (repetition time [TR] 2300 ms, echo time [TE] 2.98 ms, slice thickness 1 mm, field of view [FOV] 256 mm, flip angle 9°, and voxel size 1 × 1 × 1 mm), high-resolution anatomical scan for template registration and gray matter volume analysis, a resting state functional MRI scan (10 minutes, echo planar imaging, EPI, TR 2000 ms, TE 28 ms, slice thickness 4 mm, FOV 220 mm, flip angle 77°, and voxel size 3.4 × 3.4 × 4 mm), an fMRI scan with blocks of painful thermal stimulation (2 runs of 8 minutes), and an fMRI scan with cognitive task (2 runs of 5 minutes 10 seconds). Parameters for pain and cognitive task scans: EPI, TR 2500 ms, TE 30 ms, slice thickness 3 mm, FOV 230 mm, flip angle 90°, and

voxel size 3 × 3 × 3 × mm. A diffusion weighted scan for diffusion tensor imaging and a resting state arterial spin labeling scan were also collected but are not analyzed here.

2.10. Voxel-based morphometry

We used voxel-based morphometry to assess longitudinal GMV changes in patients as well as to assess differences between patient treatment groups over time.[4] All images were realigned to the anterior–posterior commissure in Statistical Parametric Mapping (SPM12) before preprocessing. The computational anatomy (CAT12) toolbox located within SPM12 was used for the longitudinal preprocessing of patient T1 images.[29] Using the longitudinal segmentation pipeline in CAT12.1 (r1278), the structural T1-weighted images acquired at each timepoint were spatially normalized to Montreal Neurological Institute (MNI) space (resampled to a voxel size of 1.5 × 1.5 × 1.5 mm), segmented into gray matter, white matter (WM), and cerebrospinal fluid (CSF). Scans were preprocessed with an absolute threshold mask of 0.1. This threshold excluded voxels with less than 10% probability of being gray matter. Finally, images were smoothed with an 8-mm Gaussian Kernel before analysis.

Quality controls of MRI images took place in 2 stages. Raw images were carefully examined for morphological abnormalities, as well as movement and scanner artifacts before preprocessing. Each image was also overlaid with the T1 template in Check Reg to assess the orientation. Postpreprocessing each image was assessed for quality using the 2 options available in CAT12.[29] We used the display all slices option in CAT12, which displays one horizontal slice for each subject and thus gives an overview of the segmentation. Any images that warranted further inspection were overlaid on the standard T1 brain in Check Reg. In addition, we used the sample homogeneity option in CAT12 and the quality measures created during preprocessing as well as nuisance parameters (age, sex, and total intracranial volume [TIV]) to get a better picture of the quality of the data. The tool displays a correlation matrix as well as overall mean correlation and weighted overall image quality.[29] The option to view the most deviating data was also used, and any images presented in this tool were further examined in Check Reg. Provided data did not have any artifacts upon further inspection they were used in the analysis.

2.11. Resting-state functional magnetic resonance imaging

Preprocessing was performed in SPM12 and included slice timing correction; realignment (motion correction); coregistration of the T1 to the mean functional image; segmentation of the T1; normalization of functional images, with interpolation to 2 × 2 × 2-mm voxels; and smoothing of 6 mm. Note that resting-state fMRI underwent additional preprocessing. Quality control steps included visual inspection of the data at each preprocessing stage. SPM12 defaults were used except in rare cases were preprocessing led to suboptimal registration or normalization.

We applied a motion regression approach based on framewise displacement using custom scripts. We removed subjects if FrameWise Displacement Arithmetic Mean was greater than 0.3.[52–54] We chose this cutoff because it seemed to consistently remove subjects whose average motion was larger than the rest of the group. We did not observe any differences in movement across sessions or conditions.

Insula seeds were selected based on the study "Decoding the role of the insula in human cognition: functional parcellation and large-scale reverse inference."[16] This article used hierarchical clustering of resting state functional connectivity of insula voxels and achieved a 3 parcellation solution: daINS, ventral anterior insula (vaINS), and posterior insula (pINS). Based on reverse inferense from neurosynth.org, vaINS was associated with affective responses, daINS with cognitive, and posterior with sensory. These regions of interest were downloaded from https://identifiers.org/neurovault.collection:13 after correspondence with the authors. The seeds were masked with the AAL2 atlas region for insula because the original ROIs extended outside of the insula.

Data processing was performed through CONN toolbox.[76] We used 5 principal components for WM and CSF using triply eroded WM and eroded CSF. In addition, we used motion parameters and first-order temporal derivatives applied linear detrending and a bandpass filter of 0.008 to 0.1 Hz (filtering applied simultaneously). Motion spikes were identified using an output from a custom script and included movement "spikes" where greater than 0.3 mm of framewise displacement occurred.

Subjects underwent first-level analysis of resting state functional connectivity for each ROI together. Group-level seed maps (1-way analysis of variance), calculated from baseline data (n = 74), were as expected (Supplementary Fig. 1, available at http://links.lww.com/PAIN/A979). Dorsal aINS was strongly linked to attention networks (dorsal attention, salience, DLPFC, and EMN). pINS was strongly connected to thalamus and sensorimotor cortex and parts of posterior MCC.[71] Ventral aINS was functionally connected with DMN and amygdala. These findings are consistent with the study from which the ROIs were taken.[16]

2.12. Multisource interference task functional magnetic resonance imaging

Participants performed a cognitive task, the MSIT task,[14] which reliably activates the MCC and EMN,[59] as reported previously.[59,63] Subjects were trained to perform the task before the scanning session and then allowed again to practice the session in the scanner before the session began. First-level analyses: 2 runs of 5 minutes 10 seconds, where each run included 5 × 20-second blocks of control, 5 × 20 blocks difficult, with 10 seconds of tapping in between each task block. Motion parameters were included in the GLM. A one-sample *t* test was used to create a baseline group MSIT map comparing the difficult and easy tasks (n = 81; Supplementary Fig. 2, available at http://links.lww.com/PAIN/A979).

2.13. Pain functional magnetic resonance imaging

Subject-specific, moderately painful (5-7 on a 0-10 numeric rating scale) temperatures were selected based on subjects' responses to prescan quantitative sensory testing and confirmed with verbal ratings once patients were inside the scanner. Thermal stimuli were applied to the left forearm using Medoc Inc Pathway with ATS 30-mm thermode. Two runs of 8 minutes where each run included 5 stimuli of 28-second ramp and hold at a nonpainful warm temperature and then at the subject-specific, moderately painful temperature. After each run, subjects verbally rated the average and maximum pain intensity on a 0 to 10 numeric scale. First-level analyses: warm and pain onset were modeled as the first 2 seconds of the stimulus, while warm and pain block were modeled as the subsequent 28 seconds. In addition, pain offset was modeled as the 2 seconds starting at the onset of descending ramp back to the 32°C (baseline). Motion parameters were included in the GLM. One-sample *t*-tests are shown for baseline (n = 77) pain onset (Supplementary Fig. 3, available at http://links.lww.com/PAIN/A979) and pain block (Supplementary Fig. 4, available at http://links.lww.com/PAIN/A979).

2.14. Statistical methods

Clinical outcomes were analyzed using the intention-to-treat approach. Effects of intervention were estimated using mixed-effects models, where patient was a random effect, and fixed factors included treatment, time, treatment-by-time interaction, age, cohort, interval in days between MRI and treatment, medication, presence of other pain, and education. Difference in treatment response rate was assessed using a generalized linear model with a logit link function. The regression model for the mean with the binomial distribution variance function was used to model the log odds ratios. The generalized linear models included the following covariates: age, medication, level of education, presence of other pain, and interval in days between MRI and first intervention. A logistic regression model predicted probability of response to treatment. *P*-values are nominal and not adjusted for multiple outcomes. Testing was two-sided and used the 0.05 level of significance, and statistical analyses used R-Studio, Version 1.1.453.

Imaging outcomes were analyzed per protocol.

2.15. Regions of interest

Our primary outcomes for MRI included: left DLPFC and EMN activation during cognitive task performance; DLPFC, cingulate, and aINS GMV; resting state connectivity of the right dorsal aINS to the left DLPFC and component regions of the EMN. Regions of interest selection was based on hypothesized areas that are involved in both pain and cognition.[59] We used the peak voxels from group-level (n = 81) MSIT activation and created a 4 mm radius sphere around each peak. The regions selected included the left and right DLPFC, left and right aINS, and aMCC. We also created a mask for all MSIT activations (EMN).[26]

Region of interest analyses used the same linear mixed models approach as used for primary clinical outcomes. Linear mixed models included patient as a random effect and fixed factors of treatment, time, and the treatment-by-time interaction, and scanner upgrade as a covariate, with bonferroni correction for multiple comparisons.

2.16. Whole-brain analyses

2.16.1. Sandwich estimator toolbox analysis

The Sandwich estimator toolbox (SwE) (version 2.0) was used to model the longitudinal changes in GMV and fMRI measures (resting state, cognitive task, pain) in patients.[35] This toolbox is specifically designed for repeated-measures MRI analysis and uses an unstructured covariance structure and a small sample adjustment. It uses an alternative to the traditional linear mixed model and uses a simple ordinary least squares marginal model for estimates of the parameters of interest. The sandwich estimator is used to calculate the standard errors of these estimates and is used in conjunction with the ordinary least squares. The flexibility of the SwE is in its robustness to misspecification of the covariance structure, and the utilization of this approach accounts for the correlations in repeated measures and can be used with unbalanced data sets with missing data.

We modeled treatment group (MBSR vs SMH) by time (baseline, week 10, and week 20) interactions to compare change in GMV and fMRI measures over time between the 2 treatments. In addition, to account for the scanner upgrade which occurred within the last year of the study and impacted the last of the 8 cohorts of patients enrolled (patients with scans conducted on both scanners), all analyses were run adjusting for this change. Secondary analysis examined the treatment and time effects.

Using the nonparametric SwE model with 10,000 bootstraps, we used a cluster-forming threshold of $P < 0.001$ and FWE (estimated from the wild bootstrap distribution) correction of 0.05 at the cluster level. The contrast of interest was the treatment-by-time interaction. Main effects of time and treatment are provided in the supplementary material.

3. Results

Among 573 individuals contacted for telephone screening, 168 were potentially eligible and 119 of these met the headache frequency criteria during baseline (**Fig. 1**). The main reasons for exclusion were not meeting migraine or headache frequency criteria, ineligible or refused MRI/pain testing, schedule incompatibility, or migraine secondary to injury. Ninety-eight participants were randomized to treatment; 50 were assigned to receive MBSR+; and 48 were assigned to receive SMH. All attended at least one session. Five participants (5%) withdrew from treatment after the first session but agreed to continue with data collection, and 3 participants (3%) withdrew from treatment and were lost to follow-up. Forty-three (86%) of the MBSR+ participants and 40 (83%) of the SMH participants completed all sessions, either in the group or individually as a make-up.

At baseline, treatment groups were similar on all sociodemographic characteristics (**Table 1**). Participants (mean age of 36 years) were predominantly female (91%), white (72%), and 80% had completed at least 1 year of college. At baseline, they reported an average of 7.8 headache days, and only 15% were using a preventive treatment for migraine. There were no group differences in treatment withdrawal or loss to follow-up.

3.1. Primary outcomes

At week 20, the MBSR+ group reported fewer headache days (4.6 [95% CI 3.6-5.6]) compared with the SMH group (6.0 [95% CI 4.9-7.0]; $P = 0.04$; **Table 2**). This effect was apparent at week 10 because the MBSR+ group reported fewer headache days (5.5 [95% CI 4.6-6.5]) compared with the SMH group (6.9 [95% CI 5.9-7.9] $P = 0.04$). This treatment effect was not significant at week 52 ($P = 0.12$).

Region of interest analyses revealed no significant treatment-by-time effects related to gray matter volume, cognitive task activation, or resting state fMRI (see the supplementary material available at http://links.lww.com/PAIN/A979). Both groups showed decreased anterior midcingulate volume ($P = 0.04$) and decreased connectivity of right daINS to cognitive task network (EMN) ($P = 0.02$) at week 20.

3.2. Secondary outcomes

At week 20, the MBSR+ group reported reduced HIT-6 scores (2.0 [95% CI 1.1-2.9]) compared with the SMH group (3.7 [95% CI 2.7-4.7]; $P = 0.04$). Headache impact did not differ between treatment groups at week 10 or week 52 (**Table 2**), and average headache pain intensity did not differ between treatment group at any timepoint (**Table 2**). At week 20, 52% of the MBSR+ group were classified as treatment responders (≥50% reduction in headache days) compared with 23% of the SMH group ($P = 0.004$; **Table 2** and **Fig. 2**), yielding a number needed to treat of 3.4. The MBSR+ group reported fewer migraine days at week 10 ($P = 0.0008$) and week 20 ($P = 0.004$) relative to SMH, but not at week 52 (**Table 2**).

Whole-brain analyses revealed a significant treatment-by-time interaction on activation during the cognitive challenge. The MBSR+ group showed decreased activation in the bilateral

Table 2

Primary and secondary clinical outcomes.

Primary clinical outcomes*			
Week	**SMH**	**MBSR+**	***P***
Headache days (per 28 d calendar)†			
Baseline	7.7 (6.7, 8.7)	7.8 (6.9, 8.8)	0.85
10	6.9 (5.9, 7.9)	5.5 (4.6, 6.5)	*0.04*
20	**6.0 (4.9, 7.0)**	**4.6 (3.7, 5.6)**	**0.04**
52	5.6 (4.6, 6.7)	4.6 (3.7, 5.6)	0.12
Secondary clinical outcomes			
HIT-6‡			
Baseline	59.6 (57.7, 61.5)	59.6 (57.9, 61.3)	0.99
10	58.5 (56.5, 60.4)	56.3 (54.5, 58.1)	0.08
20	**57.5 (55.5, 59.4)**	**54.6 (52.9, 56.4)**	**0.02**
52	58.4 (56.4, 60.4)	56.2 (54.4, 58.1)	0.10
Pain severity§			
Baseline	4.3 (3.8, 4.8)	4.7 (4.2, 5.2)	0.20
10	4.4 (3.9, 4.9)	4.4 (4.0, 4.9)	0.62
20	4.4 (3.9, 5.0)	4.4 (4.0, 4.9)	0.63
52	4.7 (4.2, 5.3)	4.5 (4.1, 5.0)	0.84
No. of responders‖ N, %; 95% CI			
20	11 (23%; 12%-37%)	26 (52%; 37%-66%)	*0.004*
Migraine days (per 28-d calendar)†			
Baseline	3.2 (2.2, 4.2)	3.3 (2.5, 4.2)	0.83
10	4.0 (3.0, 5.0)	1.9 (1.0, 2.8)	*0.0008*
20	3.7 (2.7, 4.7)	2.0 (1.1, 2.9)	*0.004*
52	3.1 (2.1, 4.0)	2.1 (1.2, 3.0)	0.12

Adjusted mean values, 95% confidence intervals. Significant values for secondary outcomes are shown in italics.
* Primary clinical outcome timepoint was week 20 (bolded).
† Adjusted for cohort, age, medication, and education level.
‡ Adjusted for cohort, age, medication, and presence of idiopathic pain.
§ Adjusted for cohort, age, medications, education level, presence of idiopathic pain, and interval days between baseline and first MBSR/SMH session.
‖ Response was defined as 50% or greater reduction in headache frequency at week 20 compared with baseline.
MBSR, mindfulness-based stress reduction; SMH, stress management for headache.

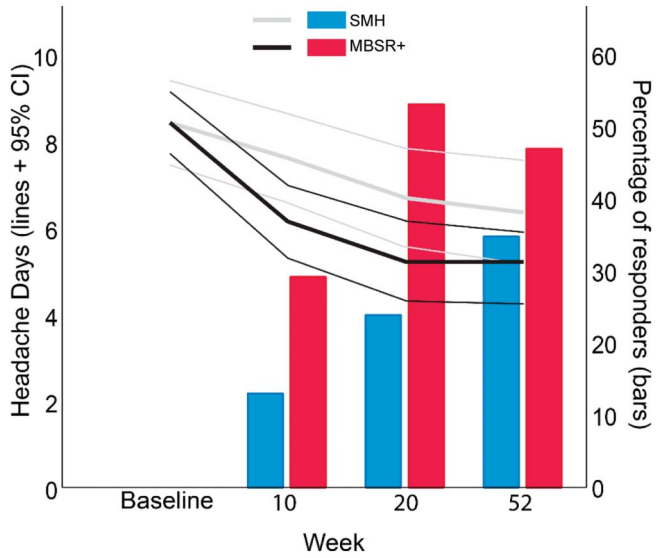

Figure 2. Clinical outcomes. Mean (thick lines; 95% confidence intervals shown in thin lines) number of headache days per 28-day diary (uncorrected values) for SMH (gray) and MBSR+ (black). Responder rates (with response defined as a 50% reduction in headache days from baseline) are shown in bar plots, with MBSR+ in red and SMH in blue. At week 20 (primary outcome), both headache frequency and response rate were significantly better in the MBSR+ group. MBSR, mindfulness-based stress reduction; SMH, stress management for headache.

cuneus and right parietal operculum at week 20 compared with the SMH group (**Fig. 3**; Supplementary Table 2, available at http://links.lww.com/PAIN/A979). Whole-brain analyses also revealed a significant interaction of left daINS connectivity to the right posterior parietal cortex and right cuneus (**Fig. 3**; Supplementary Table 2, available at http://links.lww.com/PAIN/A979). There were no significant interaction effects for the other 5 insula seed regions, gray matter volume, or activation during pain stimulation for the whole-brain analyses.

3.3. Adverse events

There were 16 adverse events reported of which 15 were mild (eg, high blood pressure, hives, and jaw pain) or moderate (eg, car accident and kidney stone); the one serious adverse event (stroke), in accordance with the data safety monitoring plan and consultation with the independent monitoring committee, was deemed unlikely related to intervention. The remaining 7 were definitely not related, 7 were unlikely related, and 1 was possibly related to study procedures (one participant reported a migraine during the MRI session).

4. Discussion

Among adults with episodic migraine, enhanced mindfulness-based stress reduction (MBSR+) decreased headache and migraine days and headache-related disability, as well as yielded a higher treatment response rate, relative to the active control (SMH). Treatment response (50% reduction in headache frequency) to MBSR+ relative to SMH yielded a number needed to treat of 3.4, which is comparable with valproic acid—one of the first-line treatments for episodic migraine prophylaxis.[45] These results hold promise for the use of mindfulness-based interventions for headache, with treatment response rates qualitatively comparable or exceeding effects of most existing standard pharmaceutical therapies in the time frames they have been tested.[1,5,6,9,11,22–24,28,46,47,56,66,67,69]

Although the effects of MBSR+ in reducing headache frequency were not significantly different from SMH at the 52-week follow-up, it is worth noting that the reduced headache frequency of 4.6 headaches in the MBSR+ group observed at post-treatment remained steady through 52 weeks (**Table 2**). What changed at 52 weeks was the headache frequency of the SMH group, which showed a slow, steady reduction in headache frequency over the course of the study, so that the difference between groups became nonsignificant at 52 weeks. A common issue in conducting clinical trials is the challenge of "regression to the mean," since study participants may be experiencing a particularly difficult period with symptoms at the time of enrollment, and the design solution is inclusion of a control group. We designed the study to include an active control group, led by an experienced nurse expert in headache management to account for the influence of expectations and nonspecific effects of intervention as well as the effects of time. This pattern of findings suggests that the SMH intervention, which included discussions of multiple headache management skills (building social support networks and managing diet, exercise, and sleep), may slowly reduce headache frequency.

Although no effects of MBSR+ training were observed on the primary neuroimaging outcomes, secondary whole-brain analyses identified 2 findings that suggest an increase in cognitive

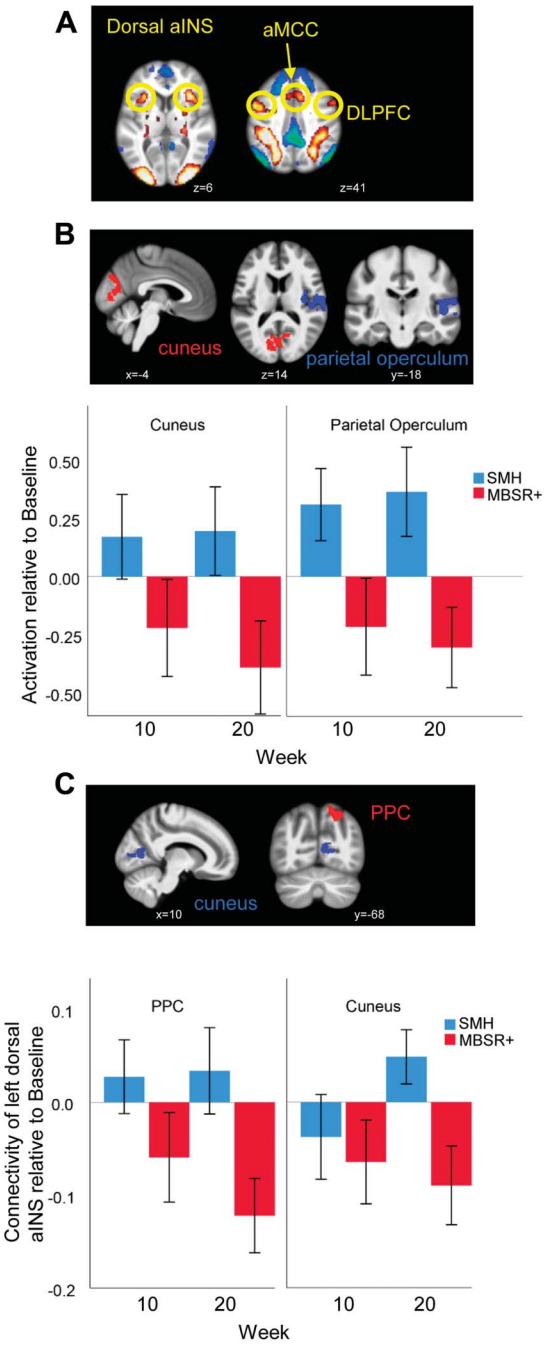

Figure 3. MRI outcomes. (A) Regions of interest for primary outcome analyses. The activation map is defined from the baseline group map (all patients) for activation during the cognitive task (difficult vs easy contrast on the multisource interference task). The circled regions show the 5 ROIs derived from this map (left and right dorsal anterior insula [aINS], left and right dorsolateral prefrontal cortex [DLPFC], and anterior MCC [aMCC]). These ROIs were used to assess the primary MRI outcomes, which included structure, resting state connectivity, and pain- and cognitive-related activation. There were no significant effects of treatment for region of interest analyses. (B) Whole-brain (secondary outcome) analysis interaction effect for cognitive task-related activation. The SwE model assesses the interaction between treatment and time for the difficult vs easy contrast on the multisource interference task. Identified regions show a decrease in activation level in the MBSR+ compared with SMH group over time. (C) Whole-brain analysis interaction effect for left dorsal aINS resting state connectivity. Regions show a decrease in activation level in the MBSR+ compared with SMH group over time. Images are displayed on the average anatomical MRI for all patients at baseline. Error bars are 95% confidence intervals. MNI coordinates are shown for each slice as x, y, or z. MBSR, mindfulness-based stress reduction; MRI, magnetic resonance imaging; ROI, Regions of interest; SMH, stress management for headache.

efficiency that is consistent with findings from the meditation literature. Compared with SMH, MBSR+ training led to decreased activation of the parietal operculum and visual cortex (cuneus) during the cognitive challenge. Both long-term meditators[8] and individuals trained in MBSR[41] show altered visual cortex connectivity and increased activation during focused attention. The parietal operculum, including posterior insula, is activated by pain and deactivated by cognitive challenge,[59] and we have previously reported that this is the only acute pain-related activation that is modulated by cognitive demand in both healthy subjects and migraine patients.[48] In addition, we observed reduced resting connectivity of the daINS to posterior parietal cortex and visual cortex (cuneus) after MBSR+ training compared with SMH. Because daINS strongly connects to the posterior parietal cortex and cuneus as part of the cognitive task network,[16] this finding supports increased cognitive efficiency after MBSR+. These increases in cognitive efficiency seen in the MBSR+ group may reflect changes due to the practice of meditation or alternatively may reflect the effect of having fewer headaches during the period surrounding measurement.

Our study examined MRI primary outcomes in a registered clinical trial for a chronic pain condition. The primary imaging outcomes, including changes in gray matter volume, activation during cognitive challenge, and resting state connectivity of the anterior insula in a priori selected ROI, did not differ between groups. The choice of these regions was based on literature when the study was proposed and our preliminary data, focusing on the DLPFC[61] and other brain areas showing pain-cognition interactions.[15,48,60,62–64] Most neuroimaging studies compare individuals with chronic pain to healthy subjects, rather than longitudinal designs examining how the brain changes with treatment. Because we did not find treatment effects in the areas that distinguish those experiencing daily pain, our findings suggest that brain changes distinguishing patients from healthy controls might not be useful as treatment targets.

Most MRI studies reporting effects of treatment have only investigated the treatment group[36,55,63,64] or treatment responders within a group exposed to treatment.[25,72,73] This study compares 2 active treatment arms and includes both treatment responders and nonresponders in the analyses. It is possible that the results from previous studies examining brain changes over time are dependent on treatment response, rather than the effects of the specific intervention itself. Future work should thus include comparisons of responders and nonresponders, as well as examining the associations between changes in clinical and neuroimaging outcomes.

These findings share limitations common to most RCTs and may have limited generalizability due to the likely selection bias that results from the strenuous requirements of participation, including time commitment and willingness to complete repeated MRI scans, resulting in most of the participants being college educated. Study strengths, in addition to the use of MRI outcomes, include one of the largest sample sizes for measuring brain imaging outcomes in migraine or any chronic pain disorder, the very small loss to follow-up, the close matching of MBSR+ to the active control, and long-term follow-up.

5. Conclusions

In episodic migraine, MBSR+ showed superior treatment effects compared with an active control, with significant reductions in headache frequency that are comparable with commonly used first-line treatments for episodic migraine prophylaxis. Brain changes in the MBSR+ group were seen in the pattern of

functional connectivity and activation during a challenging cognitive task that are consistent with increased cognitive efficiency. These findings suggest that MBSR+ can be an effective prophylactic treatment option for episodic migraine.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/A979.

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