Official Title: Mindfulness and Mechanisms of Pain Processing in Adults With Migraines
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Study Site

Wake Forest School of Medicine
Department of Neurology
Wake Forest Translational Science Clinical Research Unit

OVERVIEW:
Part 1 of this study is a cross-sectional study evaluating the pain responses of migraineurs compared to healthy controls. Part 2 is a randomized clinical trial of Mindfulness Based Stress Reduction in migraineurs. Part 1 will include both healthy volunteers and migraineurs while Part 2 will only include migraineurs. Migraineurs may participate in both parts of the study.

The protocol is split into Part 1 and Part 2.

PART 1

PRÉCIS

Title: **Mindfulness and Mechanisms of Pain Processing in Adults with Migraines**

Primary Objective of this study**:** Assess experimental heat pain responses (pain intensity, pain unpleasantness, pain catastrophizing, emotional reactivity) in migraineurs vs. healthy controls.

Design and Outcomes

To accomplish this objective, we will conduct a cross-sectional study in migraineurs (interictally, i.e., between migraine attacks) and healthy controls to compare responses to experimental heat pain intensity and unpleasantness and correlate these results to differences in emotional reactivity and pain catastrophizing.

Outcomes: Stimulus-response curves will be generated for each subject using the logarithmic equation: *log (VAS pain ratings)=log (t – 35) * coefficient + intercept* where t represents stimulus temperature.[1] The coefficient and intercept generated for heat pain intensity and heat pain unpleasantness will both be used as outcome variables, as well as scores from the Pain Catastrophizing Scale (PCS)[2], and the Difficulty in Emotion Regulation Scale (DERS).[3]

Interventions and Duration

Participants will complete ONE study visit where they will complete the PCS and DERS instruments and will complete Quantitative Sensory Testing (QST) pain measurements. We will compare responses to experimental heat pain intensity and unpleasantness on both migraineurs and healthy controls to compare and correlate these results to differences in their emotional reactivity and pain catastrophizing.

Sample Size and Population

The subject population consists of 98 participants (49 migraineurs and 49 healthy controls) who will be recruited for Part I. Participants will be of any gender and ethnicity. Migraineurs will be recruited through the Department of Neurology, Internal Medicine, Family Medicine, and the Emergency Department from Wake Forest School of Medicine. In addition, recruitment will occur from Dr. Timothy Houle's Headache research program, via Wake Forest's electronic medical record system, advertisements/flyers and the Downtown Health Plaza (DHP). Healthy Controls will be recruited from the greater Winston-Salem area through IRB-approved local flyers (posted at the four local colleges, including Wake Forest University), advertisements placed online (e.g. Craigslist) and in local newspapers (e.g. the Winston-Salem Journal), and through the Wake Forest Baptist Hospital institutional database of research volunteers. Interested persons will contact the study staff for a telephone screen. A study cell phone will be set up so that interested persons can call at any time. The phone will be secured and encrypted via our AirWatch Mobile Device Management solution.

All referring providers will be invited to a presentation to thank them for their assistance and to present the data results from the study. At the presentation, the referring providers will be entered into a drawing for a $100 gift card whether the referred subject enrolls in the study or not.

To ensure comparable groups, migraineurs and controls will be matched on age (±5 yrs), gender, and race.

STUDY OBJECTIVES

Primary Objective

Primary Objective of this study**:** To assess experimental heat pain responses (pain intensity, pain unpleasantness, pain catastrophizing, emotional reactivity) in migraineurs vs. healthy controls.

Hypotheses: Migraineurs will report higher pain intensity and pain unpleasantness levels in response to experimentally induced pain than controls; (1b): Pain catastrophizing and emotional reactivity will moderate the association between pain unpleasantness and pain intensity; (1c): Pain catastrophizing and emotional reactivity scores will be positively associated with pain unpleasantness levels.

BACKGROUND AND RATIONALE

Background on Condition, Disease, or Other Primary Study Focus

Migraine is common and disabling. Migraine affects 36 million Americans and costs $15 billion/year due to lost workdays, diminished productivity, and increased health care utilization.[4-6] Affective/cognitive processes such as pain catastrophizing and emotional reactivity often play a major role in migraine pain and disability and may be just as important to target as the sensory aspect. High pain catastrophizing, a maladaptive cognitive process of exaggerated pain rumination,[7-11] is associated with more pain and disability across clinical pain syndromes, including headache.[12-21] Affective disturbance is highly comorbid with migraine and associated with migraines becoming chronic.[22-25] Due to this cognitive/affective load that builds over time in migraine, we hypothesize that migraine alters the relationship between the sensory and affective dimensions of pain processing.

Study Rationale

Our current tools of migraine pain measurement are inadequate to distinguish the overall burden of suffering, as there is an over reliance on a single numerical pain score to represent the entire pain experience. For example, one patient with a level 8/10 migraine pain may still be functioning at work while another may be writhing in bed at home, completely disabled. Measuring and targeting the affective component, in addition to the sensory component of pain, may capture this discrepancy in disease burden. In the chronic pain world, distinguishing between the sensory and affective components of pain has yielded useful insights. For example, cancer pain is impacted by high affective pain ratings while musculoskeletal pain has much lower affective pain ratings. Interestingly, this work has not been extended into the migraine world, as though migraine pain is viewed as a purely sensory pain experience. If affective mechanisms are, in fact, more important than previously realized, this could explain the excess burden of migraine in people with comorbid affective conditions like anxiety, depression, and with past histories of emotional or sexual abuse. The affective component of migraine pain may be just as important as the sensory component to target and measure since it significantly impacts outcomes, disability, and has therapeutic treatment implications.

Quantitative sensory testing (QST) is a robust lab paradigm (not a clinical experience) that delivers one painful noxious thermal stimuli and asks for simultaneous pain intensity and pain unpleasantness scores. By using this in our research, we will be able to differentiate the sensory (pain quality—what the pain feels like) from the affective (how awful/unpleasant the pain feels) components of experimental pain in normal controls vs. migrainuers. If there is a difference between QST measurements in healthy controls vs. migraineurs, an intervention's impact could be determined if it brings migraineurs' QST results closer to healthy controls' QST results. QST results could become a marker of migraine activity. Affective components of pain may be targeted in ways that do not involve medication, which is highly desirable in a condition that is persistent throughout a lifetime and principally affects women of childbearing potential. In summary, distinguishing the sensory from affective components of pain in our research will help us determine if QST measurements can be used as a marker of migraine activity.

Migraineurs may process noxious stimuli differently than healthy non-migraineurs,[26] but we do not fully understand this difference. Using acute experimental pain in adults with clinical headache pain may help us understand the cognitive and affective mechanisms involved in both types of pain processing. This study will help disentangle the sensory (pain intensity) and affective (pain unpleasantness) components that comprise the subjective pain experience and we will be able to compare these components in migraineurs vs. healthy controls.

We hypothesize that having migraine affects the relationship between the sensory and affective dimensions of pain processing, and this relationship is moderated by these affective/cognitive

factors that build over time in migraineurs (e.g., pain catastrophizing and emotional reactivity). We will assess this hypothesized difference directly by evaluating pain intensity (sensory component of experimental pain) and unpleasantness (affective component of experimental pain). Interestingly, migraineurs exhibit lower thermal pain and tolerance thresholds, lower mechanical pain thresholds, enhanced pain expectation, and deficits of conditioned pain modulation and habituation.[26-32] When compared to healthy controls, we hypothesize that: (**Figure 1)** A) migraineurs will exhibit significantly higher pain reports in response to experimentally induced pain; B) pain catastrophizing and emotional reactivity will moderate the association between pain unpleasantness and pain intensity; and C) the affective/cognitive factors (**Figure 1, Box A**) will be positively associated with pain unpleasantness.

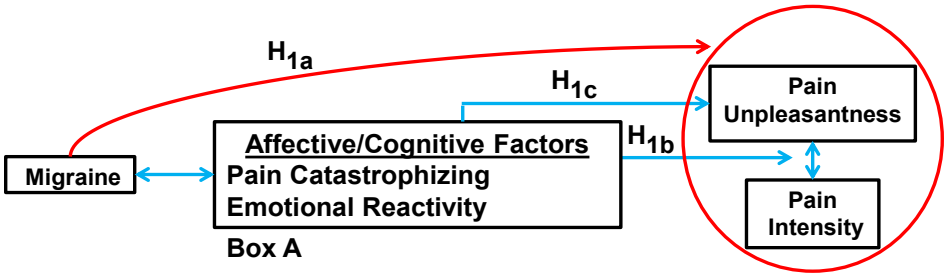


Figure 1
***Theoretical* Model of Experimental Pain Responses in Migraineurs.**
H_{1a}, H_{1b}, and H_{1c} refer to the corresponding Hypotheses from Aim 1

No previous studies have evaluated differences in experimental pain intensity vs. pain unpleasantness in migraineurs vs. controls. As migraine pain uniquely involves many altered sensory phenomenon (e.g., photophobia, phonophobia), it cannot be assumed that responses to experimental pain in migraine will be the same as other clinical pain syndromes. Further, different clinical pain syndromes have distinct responses to pain intensity vs. pain unpleasantness.[33]

STUDY DESIGN

We will conduct a cross-sectional study in migraineurs (interictally, i.e., between migraine attacks) and healthy controls to compare responses to experimental heat pain intensity and unpleasantness and correlate these results to differences in emotional reactivity and pain catastrophizing.

SELECTION AND ENROLLMENT OF PARTICIPANTS

Inclusion Criteria

Inclusion criteria for Healthy Controls: ≥18yo; pain free and healthy, without any major medical or psychiatric conditions
Inclusion Criteria for Migraineurs: ≥18yo with >1 yr of migraines and currently 4-20 days/month with migraines, although no migraine the day of study visit (see Table 1 for migraine diagnosis) or pain relieving medications within 12 hours of study visit.

Exclusion Criteria

Exclusion criteria for Healthy Controls: Diagnosis of migraine, probable migraine, Current regular (weekly or more often) practice of meditation or other mind-body intervention or frequent headaches of any type other than tension-type headaches on three or fewer days/month.

Exclusion criteria for both: Any major unstable medical/psychiatric illness (e.g., hospitalization within 90 days, suicide risk, etc.); severe clinical depression/anxiety (with PHQ-9 scores >20); chronic pain condition (e.g., fibromyalgia, migraines for healthy controls, etc.) or sensory abnormalities (e.g., neuropathy, Raynaud's, etc.); current regular (weekly or more often) practice of meditation or other mind-body intervention; diagnosis of medication overuse headache or chronic migraine. Migraineurs will be studied if they have been headache-free the day of the study visit. Participants may be currently taking migraine medications, as long as they do not have a diagnosis of medication overuse headache. Volunteers with no pain ratings to frankly noxious stimuli (temperatures > 49°C) or excessive responses to threshold temperatures (~43°C) will be excluded. Pregnant subjects will be excluded from all portions of the study due to possible unknown risks of frankly noxious stimuli. Due to unknown risks and potential harm to the unborn fetus, sexually active women of childbearing potential must use a reliable method of birth control while participating in this study. Reliable methods of birth control are: abstinence (not having sex), oral contraceptives, intrauterine device (IUD), DepoProvera, tubal ligation, or vasectomy of the partner (with confirmed negative sperm counts) in a monogamous relationship (same partner). An acceptable, although less reliable, method involves the careful use of condoms and spermicidal foam or gel and/or a cervical cap or sponge.

Table 1: **Migraine Diagnosis***

- At least 5 attacks, not attributable to another disorder, with:
  - Headache lasting 4-72 hours (untreated or unsuccessfully treated)
  - Headache with at least 2 of the 4:
    - Unilateral location
    - Pulsating quality
    - Moderate or severe pain intensity
    - Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)
  - During headache at least 1 of the 2:
    - Nausea and/or vomiting
    - Photophobia and phonophobia

*According to the International Classification of Headache Disorders-II Guidelines

Study Enrollment Procedures

The subject population consists of 98 participants (49 migraineurs and 49 healthy controls) who will be recruited for Part I. Participants will be of any gender and ethnicity. To ensure comparable groups, participants and controls will be matched on age (±5 yrs), gender, and race. We have obtained IRB approval for all recruitment procedures (Wake Forest IRB protocol # IRB00027845).

Participants with migraines will be recruited through several different mechanisms 1) Wake Forest Departments of Neurology, Internal Medicine, Family Medicine and Emergency Department; 2) Wake Forest Houle Headache Research Center 3) Wake Forest Electronic Medical record system; 4) Local flyers, radio/television/newspaper advertisements. The primary source of recruitment will be through the Wake Forest Department of Neurology clinics.

The primary source of recruitment will be through the Wake Forest Department of Neurology clinics. Dr. Wells has her own headache clinic within the department, where she has seen over 300 headache patients in the last year (on average 9 new and 6 follow-up patients per week). Patients will also be recruited through the Wake Forest primary care clinics. Flyers will be placed throughout the hospital and specifically in the clinics of Neurology, Internal Medicine, OB/Gyn, and Family medicine and in the Emergency Department. On average, Wake Forest sees >800patients/year in the Emergency Department with a diagnosis of migraine.

Presentations made to medical students, residents, and faculty at Wake Forest in these departments to further inform clinicians about the trial and invite them to refer eligible patients. Further, four research assistants are available through the WF emergency department and actively screen patients 6 days/week, 18 hours/day (108 hours/week). The Houle Headache Research Center has a successful record of recruiting headache patients for clinical research, recruiting 3-5 headache patients/week over the last 5 years. Wake Forest has a newly implemented electronic record system, "WakeOne" (an Epic program), and with IRB approval, we can query our Translational Data Warehouse for all patients seen at Wake Forest with a diagnosis of migraine (ICD-9 code 346) and then be able to securely have access to their data to be able to contact them. Conducting such a search reveals 17,494 records of patients with a diagnosis of migraines seen at Wake Forest in the past five years. Finally, we will use multiple local advertising mechanisms to recruit participants, such as local newspapers (e.g. Winston Salem Journal), magazines (Forsyth Woman, etc.) local National Public Radio service, local television network stations, press releases, and social media (Facebook, etc.). For adults with migraines, "opt-out" letters will be sent to potential participants and then they will be contacted by study staff for a telephone screen.

Healthy Controls will be recruited from the greater Winston-Salem area through IRB-approved local flyers (posted at the four local colleges, including Wake Forest University), advertisements placed online (e.g. Craigslist) and in local newspapers (e.g. the Winston-Salem Journal), and through the Wake Forest Baptist Hospital institutional database of research volunteers.

Screening Process-Telephone Screen:
A study investigator will contact interested participants for a pre-screening telephone interview. At the beginning of the phone call, potential subjects will be informed of the nature and sensitivity of the questions, asked whether this is an appropriate time for them to answer these questions, and told how long the phone call is expected to take. Participants will be offered the option of completing the pre-screening in person, if they wish and if it is feasible. The pre-screening telephone interview will be performed to explain the protocol, determine eligibility, discuss informed consent, and answer questions. If eligible, they will then be offered participation. Those interested and eligible will be either immediately scheduled for a screening visit or will be called in the future to set it up. A letter will then be sent to them, with the consent form attached for review ahead of time if they would like, in advance of their study visit.

Consenting procedures:
We will obtain consent before the experiment begins at the study visit. At the onset of the study visit, participants will be provided informed consent by the PI or a qualified study team member. The consenting process will occur in a private clinic room. Subjects will be given time to ask questions and can discuss with family members. The consent form states the title and purpose of the study, an estimate of how many people may enroll, the duration of participation, the procedures that will be followed, any reasonably foreseeable risks or discomforts, and benefits to the participants or others that may be expected from the research. Information is provided about the disclosure and confidentiality of protected health information they will provide, that there is no cost to participants in the study, who sponsors the study, what happens if they experience an injury or illness as a result of participating, and whom to call if they have a question or problem. Participants will be informed of payment ($40 for completion of the study visit). The telephone number of the Chairman of the Institutional Review Board will also be included for questions regarding rights as research subjects. The consent form will be signed and dated by the participant and by the person obtaining consent. The consent form has been approved by Wake Forest IRB (IRB protocol # IRB00027845).

Screening

Screening evaluations that will occur at the study visit for inclusion/exclusion include:

- Full Neurology evaluation to confirm diagnosis and inclusion/exclusion criteria

STUDY INTERVENTIONS

Interventions, Administration, and Duration

There will only be ONE study visit, which will have 3 parts.

Study Visit (Parts A, B, C):

Part A: Participants will meet with a member of the study team to: 1) review study protocol; 2) obtain informed consent; 3) obtain detailed health history/exam to confirm inclusion/exclusion criteria.

Part B: Psychological Measures: Before the experimental session, participants will use REDCap to complete the questionnaires (see Table 6 for migraineurs and Table 7 for healthy volunteers).

Part C: Experimental Session of Quantitative Sensory Testing (QST) Measurements:

Thermal Probe: MEDOC TSA-II will deliver thermal stimuli with a 16 x 16 mm thermal probe. All temperatures will be < 50°C and no stimulus as designed produces tissue damage. We have significant experience using this technique and probe with no adverse events (Coghill's lab on > 750).

Psychophysical Training: To gain experience rating pain, subjects will be familiarized with 32, 5-second duration stimuli (35 to 49°C) with the Visual Analogue Scale (VAS), a 15 cm plastic sliding scale used to quantify pain sensation intensity and degree of unpleasantness.[37] The VAS is an ideal pain measurement scale because of its ratio scale properties combined with its ease of administration and scoring.[38] The minimum rating is "no pain sensation" or "not all unpleasant" whereas the maximum is designated as "most intense imaginable" or "most unpleasant imaginable." The training will be conducted on the left arm, a location away from increased sensitivity/allodynia of head/neck regions often seen in patients with migraines.

Pain Threshold Assessment: The temperature of the probe will begin at 32°C and will increase at a rate of 0.5°C per second. The subject will be instructed to verbally respond when he or she first detects a sensation of pain. The thermode will return to baseline once the button is pressed. This will be performed up to four times, and the heat pain threshold will be determined as the average of the temperatures at which the stimulus was first perceived as painful (Yarnitsky and Sprecher, 1994). Stimulus temperatures employed for pain threshold testing will not exceed 50°C. This will be conducted on the right arm.

Experimental Session: We will administer the noxious thermal stimulation on the right calf by starting at 35°C and increasing with a 6°C rise/fall rate with a 5 second plateau up to the randomly administered temperatures of 43, 45, 47, and 49°C. Each temperature will be repeated x 3 and delivered pseudorandomly. To minimize sensitization, habituation, and hyperalgesia, all trials will be separated by 30 seconds and systematically distributed over the calf to minimize repetitive stimulation of the same skin site.[1,37,39] Perception of intensity and unpleasantness will be measured with the VAS scale after each temperature. Each series will be repeated twice. Dr. Wells has been trained in the performance and analysis of QST measurements.

The specified arm/leg positioning of the probe may be adjusted if needed.

Handling of Study Interventions

N/A

Concomitant Interventions

Allowed Interventions

Participants may continue all current treatments for their migraines while participating in this study.

Required Interventions

To participate in the study, patients must not currently have a migraine at the time of the study visit; migraineurs will be studied if they have been headache-free the day of the study visit. If participants arrive at the study visit and actively have a headache, they will be re-scheduled for completion of the study visit when headache-free.

Prohibited Interventions

N/A

Adherence Assessment

The survey assessments will be completed using REDCap and study personnel will ensure all questions are answered before participants leave each session. Study personnel will also be conducting the QST pain assessments so adherence to both pain testing and survey assessments will be high.

STUDY PROCEDURES

Table 2- Summary of Schedule of Evaluations-Part I

Task	Telephone Screen	Study Visit
Confirm Eligibility	**X**	**X**
Review Study Protocol	**X**	**X**
Sign Informed Consent Form		**X**
Health history/exam to confirm inclusion/exclusion criteria		**X**
Complete Questionnaires		**X**
QST Measurements		**X**

QST: Quantitative Sensory Testing

Description of Evaluations-See above in Study Enrollment Procedures and Study Interventions

SAFETY ASSESSMENTS

Experimental Heat Pain Assessments: The quantitative sensory testing may cause brief pain, but all temperatures will be < 50°C and no stimulus as designed produces tissue damage. The thermal probe used for this experiment, MEDOC TSA-II, will deliver thermal stimuli with a 16 x 16 mm thermal probe. The pain stimuli are chosen so that most people can tolerate them. These stimuli have been used for many years with no harmful physiological or psychological complications. However, the heat may cause redness of the skin for up to several hours, but does not cause any blistering.

The subject can easily pull away from the device if the feeling is not tolerable. The laboratory staff are experts in conducting the heat-pain intervention and the temperature of the thermal heat probe will be monitored at all times. Dr. Coghill's lab has conducted this procedure on over 750 participants and no serious adverse events have been associated with this device. A computer controlled device that touches the skin is used to apply the heat used for sensory testing. In extremely rare cases, the computer controlled stimulator has been reported to malfunction and to cause a burn to the small skin region being tested. Since this device will not be strapped to the participant's leg or arm, the participant can easily pull away from this device and stop stimulation at any time.

Reporting Procedures
We will promptly report any unanticipated problems, serious and unexpected adverse events, deviations or protocol changes to the IRB and Data Safety and Monitoring Board (See Data Safety and Monitoring Board for more details).

Serious adverse events (SAEs) that are unanticipated, serious, and possibly related to the study intervention will be reported to the I-DSMB, Wake Forest School of Medicine IRB, and NCCIH in accordance with requirements.

Unexpected fatal or life-threatening AEs related to the intervention will be reported to the NCCIH Program Officer within 7 days. Other serious and unexpected AEs related to the intervention will be reported to the NCCIH Program Official within 15 days.

Anticipated or unrelated SAEs will be handled in a less urgent manner but will be reported to the I-DSMB, Wake Forest School of Medicine IRB, NCCIH, and other oversight organizations in accordance with their requirements. In the annual AE summary, the I-DSMB Report will state that they have reviewed all AE reports.

The WFSM Institutional Data & Safety Monitoring Board (I-DSMB) will monitor the study for purposes of evaluating participant safety and study integrity. The I-DSMB is a Dean-appointed, multi-disciplinary, standing committee that is available to provide independent oversight for human research studies conducted by WFSM or by WFSM-affiliated faculty investigators. The board will review the progress of and safety for the study on a regular basis as seen below in the table 3. The DSMB will meet to review safety data at least once annually while the study has active participants, even if the prespecified review targets, as specified above, have not been met. There will be no fee for the independent monitoring of the study. All protocol deviations and adverse events will be promptly reported to the I-DSMB as well the IRB. See DSMB plan for more details.

Table 3-Safety Reporting of Data

Data type	Frequency of review	Reviewer
Subject accrual (including compliance with protocol enrollment criteria)	Quarterly	PI, DSMB
Status of all enrolled subjects, as of date of reporting	Quarterly	PI, DSMB
Adherence data regarding study visits and intervention	Bi-annually	PI, DSMB
AEs	Bi-annually	PI, DSMB

Data type	Frequency of review	Reviewer
SAEs	Per occurrence	PI, DSMB, NCCIH

STATISTICAL CONSIDERATIONS

General Design Issues

Hypothesis 1a: Adults with migraines will have a greater response to experimental pain than healthy controls.
Hypothesis 1b: Adults with migraines will have higher levels of pain unpleasantness after controlling for pain intensity compared to controls.
Hypothesis 1c: Adults with the highest pain catastrophizing and emotional reactivity scores will have the highest levels of pain unpleasantness.

Sample Size and Randomization

Sample Size Calculation: Using the marginal benefit formula for repeated measures (Vickers),[40] and assuming an average within-person correlation between repeated measurements of 0.5, a sample size of 48/group will give us 80% power to detect an effect size as low as d=0.62 for the group main effect (Hypotheses 1a and 1b). Thus, if the average VAS rating in the controls is 3 (±2 SD), we will be able to detect a VAS rating of 4.24 in migraineurs; smaller differences are unlikely to have clinical significance. For hypothesis 1c, 98 participants will also give us 84% power to detect a bivariate correlation of at least 0.4 between pain catastrophizing scores or emotional reactivity scores and pain unpleasantness levels (r≤0.4 not likely of clinical significance).

Outcomes

Stimulus-response curves will be generated for each subject using the logarithmic equation: *log (VAS pain ratings)=log (t – 35) * coefficient + intercept* where t represents stimulus temperature.[1] The coefficient and intercept generated for heat pain intensity and heat pain unpleasantness will both be used as outcome variables, as well as scores from the PCS and the DERS.

Data Analyses

Statistical Analyses: We will use mixed effects hierarchical regression models with a distribution and link function appropriate to the outcome (e.g., the best fitting distribution as defined by model selection). Repeated measures within each participant (i.e., experimental trials within a session) will be handled using subject-level random effects. We do not expect missing data for this Aim, given the controlled nature of the experimental session and electronic data capture. The specific analyses are outlined for each hypothesis:

Analyses 1a: We will separately regress the individual pain outcomes (pain intensity, pain unpleasantness) on the factorial effects for group (migraine, control), stimulus (43, 45, 47, and 49 C), and repeated experimental block (1, 2, and 3). Absent any higher order two-way (e.g., group x stimulus) or three-way (e.g., group x stimulus x block) interaction involving group, we will interpret a statistically significant group main effect as evidence that the two groups differ in their experimental pain reports.

Analyses 1b: We will run the same model as 1a but exclusively using pain unpleasantness as the outcome. We will add pain intensity as a predictor, to "control" for pain intensity reports. In this way, we will examine group differences in pain unpleasantness after controlling for pain intensity ratings (i.e., do the groups differ in degree of unpleasantness after accounting for the sensory aspect of the stimulus?)

Analyses 1c: We will regress pain unpleasantness on stimulus, block, and pain intensity ratings, but will also add catastrophizing and emotional reactivity scores as subject-level predictors. A statistically significant effect for the predictor (catastrophizing or emotional reactivity) will be interpreted as support for an association between the predictor and outcome (pain unpleasantness).

DATA COLLECTION AND QUALITY ASSURANCE

Research material obtained from human subjects (specimens, records, data).
The study data will be collected and managed using REDCap electronic data capture tools hosted at Wake Forest School of Medicine.[41] REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

PARTICIPANT RIGHTS AND CONFIDENTIALITY

Institutional Review Board (IRB) Review

Informed Consent Forms
IRB approval of these procedures has been obtained (IRB protocol # IRB00027845). Prior to participating in any phase of these studies, informed consent will be obtained from all subjects by personnel directly associated with this study. All procedures and risks will be fully explained to subjects. Informed consent from healthy subjects will be indicated/documented by the subject's signature on a consent form. Subjects will also receive a copy of the consent form. Subjects will be recruited for studies via postings on campus, Internet advertisements, and other printed advertisements in the community. If necessary to obtain adequate minority representation, under-represented racial groups will be targeted specifically for recruitment.

Participant Confidentiality and Data Storage
Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. Storage of all data will be electronically entered on a password protected network drive. To help ensure subject privacy and confidentiality, only a unique study identifier will appear on the data collection form. All question and answers will be recorded by research assistants, placed in confidential subject folders, and stored on a separate master log. Any collected patient identifying information corresponding to the unique study identifier will be maintained on a separate master log. The master log will be kept secure, with access limited to designated study personnel. Following data collection subject identifying information will be destroyed at the earliest opportunity, consistent with data validation and study design, producing an anonymous analytical data set. Data access will be limited to study staff. Data and records will be kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

Per copyright agreement for the Social Connectedness Scale-Revised (SCS-R), the PI has agreed to send de-identified results of the SCS-R and basic demographics to the author of the measure for possible secondary data analysis.

Conflict of Interest: There are no conflicts of interest.
Benefits to Participants

This study does not present the prospect of direct benefit to the participants. However, the study will provide the opportunity to gain a better understanding of how migraine affects pain processing.

PUBLICATION OF RESEARCH FINDINGS
We plan to publish our findings in top-tier scientific, peer-reviewed journals.

PART 2

PRÉCIS

Objectives

Primary objective: Test the impact of MBSR in adults with migraines on clinical headache pain.

Secondary Objectives: Test the impact of MBSR in adults with migraines on experimental heat pain, mindfulness, pain acceptance, pain catastrophizing, emotional reactivity, and headache-related disability compared to an education control group; determine factors that predict MBSR response on migraine pain.

Design and Outcomes

We will conduct a prospective, randomized controlled trial in 98 adults with migraines randomized to either MBSR or a migraine/stress education control group to assess the impact of MBSR on the sensory and affective aspects of clinical and experimental pain in adults with migraines and to determine predictors of clinical efficacy

Interventions and Duration
Participants will be randomized to either an Mindfulness Based Stress Reduction Course (MBSR) or an Education control group; both will meet weekly for 2.5 hours for 8 weeks, and may be assigned daily homework of approximately 30 minutes/day. MBSR is a standardized course in mindfulness mediation and yoga and the control group will be educated about migraine pathophysiology, headache triggers, stress, gentle stretches, and daily migraine readings. The goal of the control group is to match the time/attention/expectation of the MBSR group, without providing key ingredients of mindfulness meditation or yoga. The control group will be taught by a health care provider trained in headache care.

Sample Size and Population

98 adults with migraines will be randomized 1:1 to either MBSR or the education control group. Migraineurs will be recruited through the Department of Neurology, Internal Medicine, Family Medicine, and the Emergency Department from Wake Forest School of Medicine. In addition, recruitment will occur from Dr. Timothy Houle's Headache research program, via Wake Forest's electronic medical record system, advertisements/flyers and the Downtown Health Plaza (DHP)

STUDY OBJECTIVES

Primary Objective

Primary objective: Test the impact of MBSR in adults with migraines on clinical headache pain.

Secondary Objectives

Secondary Objectives: Test the impact of MBSR in adults with migraines on experimental heat pain, mindfulness, pain acceptance, pain catastrophizing, emotional reactivity, and headache-related disability compared to an education control group; determine factors that predict MBSR response on migraine pain.

BACKGROUND AND RATIONALE

Background on Condition, Disease, or Other Primary Study Focus

Migraine is common and disabling, affecting 36 million Americans and costing $15 billion/year due to lost workdays, diminished productivity, and increased health care utilization.[4-6] Affective/cognitive processes such as pain catastrophizing and emotional reactivity often play a major role in migraine pain and disability and may be just as important to target as the sensory aspect. Due to this cognitive/affective load that builds over time in migraine, we hypothesize that: A) migraine alters the relationship between the sensory and affective dimensions of pain processing; and B) therapies like Mindfulness-Based Stress Reduction (MBSR) that target these factors may be especially beneficial and may differentially influence the affective component of migraine. MBSR is a standardized course in mindfulness meditation and yoga with beneficial effects on many health outcomes,[42] including chronic pain.[43-49]

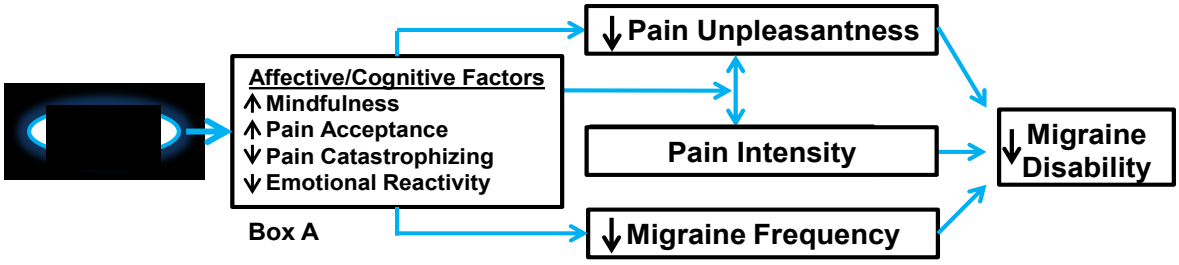
Study Rationale

Meditation differentially decreases affective (i.e., pain unpleasantness) over sensory (i.e., pain intensity) dimensions of experimental pain[50-56] and reduces pain by engaging brain regions important for the cognitive and affective modulation of pain.[51,53,55-57] Our pilot trial demonstrated the safety, feasibility, and beneficial effects of MBSR on migraines.[58] MBSR may prevent migraines by decreasing emotional reactivity (e.g., affective responses to stress),[59-63] and stress is a well-known migraine trigger.[64-66] MBSR may also train migraineurs to practice non-judgmental awareness of sensory events, reducing the affective dimension of pain more than the sensory component, and this effect may be greater in those with a greater affective pain component. By measuring both experimental and clinical pain, we will be able to test these hypotheses. Further, understanding predictors of response would improve clinical utility.

Affective components of pain may be targeted in ways that do not involve medication, which is highly desirable in a condition that is persistent throughout a lifetime and principally affects women of childbearing potential. Research has demonstrated that meditation, a non-pharmacological intervention, differentially decreases the affective over sensory responses to experimental pain in healthy controls. After learning to meditate, one's experience of pain is altered, with diminished affective responses to pain. We will be able to evaluate this effect in the clinical pain condition of migraine by determining if a meditation intervention taught to migraineurs differentially decreases the affective responses over the sensory responses to experimental pain. This work will be a novel contribution that demonstrates the specific mechanisms of meditation-induced pain relief in migraine patients. In summary, distinguishing the sensory from affective components of pain in our research will help us determine if QST measurements can be used as a target for treatment. This ultimately will help us further understand the mechanisms of meditation induced pain relief and allow for more precise, targeted treatment options.

Further, medications alone rarely target the affective/cognitive processes that often play a major role in migraine pain and disability. Because of this high affective/cognitive burden of migraine pain, we hypothesize that therapies that target these factors may be especially beneficial and may differentially impact the affective component of migraine pain. For example, cognitive behavioral therapy (CBT) is efficacious (with Grade A evidence) for migraine prevention.[67-70]

Mindfulness-Based Stress Reduction (MBSR) has beneficial effects on many health outcomes, including chronic pain conditions.[42-49,71-74] MBSR is a standardized course in mindfulness meditation and yoga.[75] Mindfulness meditation involves both 1) focused attention on a sensation like the breath while non-judgmentally disengaging from distracting thoughts; and 2) open monitoring, with non-reactive present-moment awareness of sensory stimuli.[76] These practices



cultivate a detached observation of sensory experiences like pain,[49,74] which may alter the pain experience, resulting in less pain unpleasantness, pain catastrophizing, emotional reactivity, and more pain acceptance.[45,59,60,62,63,77] The active mental training of meditation may also foster a non-reactive approach to life stressors. This may decrease emotional reactivity (e.g., affective responses to stress),[59-63] thereby decreasing the likelihood of triggering a migraine from stress (a common migraine trigger).[64-66] Further, meditation differentially decreases affective (pain unpleasantness) over sensory (pain intensity) response to experimental pain[50-56] and engages brain regions important for the cognitive and affective modulation of pain.[51,53,55-57,78,79] Based on this research and the models developed by Jensen,[80] Day et al,[81] and Price,[82] we created a simplified *theoretical* model of mechanisms of migraine pain relief from MBSR (**Figure 2**). By targeting affective/cognitive factors (**Figure 2, Box A**), we hypothesize that MBSR: A) prevents migraines from occurring, decreasing migraine frequency; B) decreases the affective components of pain so even when migraines do occur, pain unpleasantness is attenuated; and C) decreases migraine disability. (**Figure 2**). We will test these hypotheses directly by measuring both experimental and clinical pain.

Figure 2
***Theoretical* Model of MBSR Mechanisms of Migraine Pain Relief**

MBSR also requires time, energy, and healthcare resources. Thus, identifying predictors of response is critically important to better target and tailor MBSR to treat migraine. For instance, pain acceptance and pain catastrophizing were the most important factors of treatment response of a mindfulness-based cognitive therapy for headache.[83] Since mindfulness meditation appears to selectively target these processes, we hypothesize that those with the highest baseline levels of pain catastrophizing, emotional reactivity, and the affective component of experimental pain will be most likely to respond to MBSR. Increases in pain acceptance and mindfulness and decreases in pain catastrophizing and emotional reactivity may be associated with decreases in clinical and experimental pain and disability after MBSR.

No previous studies have used experimental pain to evaluate mechanisms of meditation on migraine. Measures of pain intensity and pain unpleasantness will assess nociceptive processing distinct from clinical pain status, providing a means to determine if clinical pain is differentially susceptible to reduction by MBSR. Further, employing experimental pain methodologies will allow us to distinguish affective from sensory processing, allowing us to test our hypotheses that MBSR reduces the affective more than the sensory experience, and this effect will be greater among patients with a greater affective component to their pain.

We will be able to determine predictors of MBSR response in migraineurs. Identifying simple and inexpensive ways to evaluate response will allow treatments to be targeted to those most likely to benefit.

PRELIMINARY STUDIES

We conducted several epidemiological studies that showed that many adults with neurological conditions, including headaches, use complementary and alternative medicine, despite a lack of evidence.[84-89] Further, in adults with migraines/severe headaches in the US, the mind-body therapies of deep breathing, meditation, and yoga are the most commonly used.[88] However, there have only been a few prior studies with non-standardized meditation and yoga interventions in migraine.[90-92] We conducted 2 randomized controlled trials (RCT) of MBSR that demonstrated the safety, feasibility, and efficacy of MBSR in adults with mild cognitive impairment[93,94] and migraines.[58] In 19 adults with migraines randomized to either MBSR (n=10) or usual care (n=9), MBSR demonstrated no adverse events, 0% dropout, excellent adherence (daily meditation average: 34±11 minutes; class average: 6/8 sessions), and promising effect sizes across several outcomes, despite being a pilot trial without adequate power (**Table 4**).[58] Theme analyses from qualitative interviews revealed that MBSR may also decrease emotional reactivity and improve pain cognitive reappraisal processes (e.g., less pain catastrophizing and more pain acceptance). The methods of this pilot trial[58] will be applied to this research. The results from this study support future studies with larger sample sizes to evaluate mechanisms.

Table 4: Improvements* in MBSR vs. Control Group after MBSR in Adults with Migraines

Measure	*Change in MBSR vs. Control, d[f]*	*95% CI[g]*	*Comment*
Headaches			Although underpowered, migraines were:
Frequency of Migraines/month	-1.4 d=0.32	[-4.6, 1.8]	-less frequent in MBSR group
Severity (0-10 scale)	-1.3 d=0.61	[-2.3, 0.1]	-less severe in MBSR group
Duration (hours)	-2.9 d=0.75	[-4.6, 0.02]	-shorter duration in MBSR group
Headache Disability Scores			
MIDAS[a]	-13 d=1.37	[-22, -1]	Headache disability decreased in MBSR group
HIT-6[b]	-5[c] d=0.91	[-11, -1.0]	Headache disability decreased in MBSR group
Additional Measures			
Self-Efficacy[d]	+13 d=0.81	[1, 30]	Self-efficacy improved in MBSR group
Mindfulness[e]	+13 d=0.80	[3, 26]	Mindfulness improved in MBSR group

*Pilot study was not powered to see differences on these outcomes; a-Migraine Disability Assessment (MIDAS), range: 0-5 (minimal), 6-10 (mild), 11-20 (moderate), >21 (severe); b-Headache Impact Test-6 (HIT-6), Range 36-78, 60+: severe impact; c-A change of 2.3 points on HIT-6 reflects the minimum important difference that reflects meaningful clinical change; d-Headache Management Self Efficacy scale, Range 0-175; e-Five-Facet Mindfulness Scale, Range 0-195; f=Cohen's d; g-Confidence Interval

STUDY DESIGN

We will conduct a prospective, randomized controlled trial in 98 adults with migraines randomized to either MBSR or an education control group. All participants will have migraines (no healthy controls).

SELECTION AND ENROLLMENT OF PARTICIPANTS

Figure 3:Part 2 Research

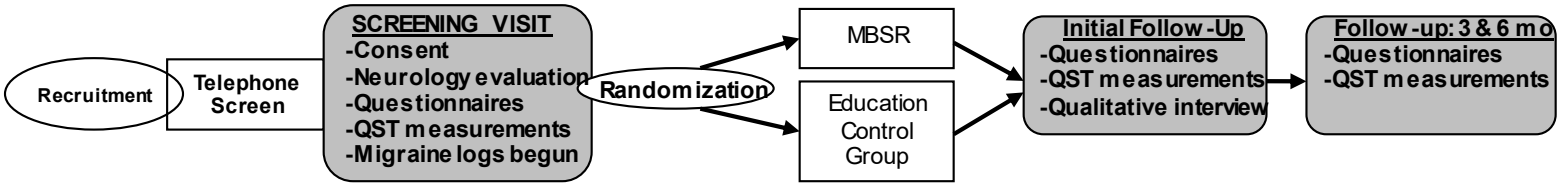


Table 5: Inclusion Criteria & Exclusion Criteria

Inclusion criteria
•Diagnosis of Migraine (see Table 1) •4-20 days/month with migraines •≥1 year of migraines •≥18 years •Able and willing to participate in 8 weekly sessions and possible daily homework 30-45min
Exclusion criteria
•Current regular (weekly or more often) practice of meditation or other mind-body intervention •Any major unstable medical/psychiatric illness (e.g., hospitalization within 90 days prior to screening, suicide risk, etc.) •Other non-migraine chronic pain condition (e.g., fibromyalgia, low back pain, etc.) or sensory nerve problems (e.g., neuropathy, Raynaud's, etc.) •Diagnosis of medication overuse headache (International Classification of Headache Disorders-II) •Volunteers with no pain ratings to frankly noxious stimuli (temperatures > 49°C) or excessive responses to threshold temperatures (~43°C) •Current or planned pregnancy or breastfeeding •Any new medication started within four weeks of screening visit •Unwilling to maintain stable current medication dosages for duration of trial •Failure to complete baseline headache logs

Study Enrollment Procedures

Recruitment: We will recruit 7 participants every 3 months over the 42 month recruitment period. The study will be run in 6 cohorts. Once ~16 participants meet criteria via phone screening, they will be re-evaluated at the in-person screening visit (see below) to ensure they still meet inclusion criteria. After the screening visit, they will begin keeping their 4 week

headache log (see below); once completed, final determination of inclusion and randomization will occur. Recruitment will continue until sample size goals are reached. We will assume ~10% dropout (conservative estimate given our 0% dropout rate in our pilot trial), so will aim to recruit 98 participants for a final sample of 88 participants. (There may be some overlap of the migraineurs with Part 1).

Screening Visit: The study staff will consent participants, confirm migraine diagnosis with history/neurological exam (will include Structured Diagnostic Interview for Headache), and have participants 1) confirm that no pain relieving medications within 12 hours of study visit, 2) complete baseline questionnaires if they have not been completed at home; 3) complete quantitative sensory testing (QST) as described in Part 1; and 4) learn how to capture daily migraine information using REDCap electronic data capture tools (or iPod touches for those without internet access). Participants will track migraines x 4 weeks to 1) confirm diagnosis; 2) confirm ability to log daily; and 3) use as the 4 week "pre-trial" baseline migraine data.

Randomization: Once 4-week migraine logs are reviewed by study staff to ensure eligibility, participants will be randomized 1:1 to either MBSR or the control group, stratified by migraine frequency (low frequency of 4-9 headaches/month or high frequency of 10-20 headaches/month). Treatment assignments will be generated by a permuted blocks method with randomly varying block size and sealed in numbered, opaque envelopes. Dr. Houle will generate the randomization (using SAS program "PROC PLAN" statement). Participants in both groups will continue to track their migraines with their daily REDCap logs for the duration of the trial.

STUDY INTERVENTIONS

Interventions, Administration, and Duration

Interventions and Interactions

The MBSR Intervention: The PI has conducted 2 previous RCTS with MBSR and is a trained MBSR instructor. The MBSR instructor for this trial (not the PI to avoid bias) has been trained in the structured protocol created by Dr. Kabat-Zinn.[95] Given the feasibility of our pilot trial, we anticipate that this population will have no difficulty engaging in the standardized protocol. The participants will meet weekly for 8 weeks for 2.5 hours, plus a "mindfulness retreat day" (approximately 6 hours) after the 6th class [9 total classes.] Mindfulness is cultivated through meditation, body scan (sequential attention to parts of the body), and mindful movement (bodily awareness during gentle stretching, based on hatha yoga). Participants can share their mindfulness experiences with others. The instructor also gives information about stress and stress relief. Participants are advised to incorporate mindfulness into their daily lives so that routine activities (brushing teeth, taking a shower, etc.) become a meditative practice. Each participant will be given the same standard guided audio recordings and encouraged to practice at home for 30-45 minutes per day, at least 5 additional days per week. Compliance will be monitored through class attendance and by daily logs of home practice (using REDCap). Once the course is completed, the participants will be advised to continue in their daily practice.

The Control Group: Migraine/Stress Education: The control group will meet for 8 weeks for 2.5 hours, plus a 1 day learning session. Content will include education about migraine pathophysiology, headache triggers, stress, and gentle stretches. The goal of the control group is to match the time/attention/expectation of the MBSR group, without providing key MBSR active ingredients of mindfulness meditation or yoga. The group will be taught by a health care provider trained in headache care.

Concomitant Interventions

Participants may stay on stable dosages of current migraine medications for the duration of the trial, but will be excluded from starting any new medication within four weeks of screening visit. This makes this study very generalizable to the general population of migraine patients seeking treatment, as most are already on some form of pharmacological treatment and will not need to stop such treatment to participate in the trial. Further, it could be dangerous for a participant to stop migraine medications as it could exacerbate their underlying headache condition.

Adherence Assessment

Adherence to the interventions will be measured by the number of weekly classes/retreat day the participants attend; participants will be considered "completers" of the intervention if they attend at least 5/9 weekly classes/retreat day. Participants who are not able to commit to at least 6/8 classes, and attend the very first class, from the onset of the study will be advised to not participate in the study, so the number of non-completers should be low.

The survey assessments will be completed using REDCap and study personnel will ensure all questions are answered before participants leave each session (See Table 8). Study personnel will also be conducting the QST pain assessments so adherence to both pain testing and survey assessments will be high.

Participants will keep daily headache logs and will receive an email via REDCap with the link to complete these logs. If a participant misses capturing a day of the log, study staff will contact the participant by phone or email and reinforce the importance of completing the daily log. Participants in the MBSR group will also keep track of their assigned home activities with a daily log in a similar way. Participants will also be contacted by phone call, letter, or email for appointment reminders.

After 8 weekly classes have concluded, study participants will be incentivized to keep daily headache logs as follows:

1. For each DAY that the participant keeps their headache log on time, their name will be entered into a drawing (will have the chance to get their name in the drawing up to 30 times in a month)
2. At the end of the month, a name will be drawn and a winner will receive a $50 Amazon gift card

STUDY PROCEDURES

Table 6 - Summary of Schedule of Evaluations – Part 1 – Migraineurs

Assessment	Telephone Screen	Study Visit
Confirm Eligibility	X	X
Review Study Protocol	X	X
Sign ICF		X
Allodynia Symptom Checklist		X
DERS		X
PCS		X
GAD-7		X
PHQ-9		X
CPAQ		X
HIT-6		X
MIDAS – one month		X
HA management self-efficacy		X
MSQOL		X
Mindfulness, FFM		X
PSS		X
Herth Hope Index		X
Life Orientation Test		X
Social Connectiveness Scale		X
Flourishing Scale		X
Brief Resilience Scale		X
NIH-Promis Measures of Sleep Disturbance		X
NIH-Promis Measures of Global Health (first question only)		X
Pittsburgh Sleep Quality Index		X
QST Measurements		X
Pain Threshold Testing		X
Vitals		X

QST – Quantitative Sensory Testing

Table 7 - Summary of Schedule of Evaluations – Part 1 – Healthy Volunteers

Assessment	Telephone Screen	Study Visit

Confirm Eligibility	**X**	**X**
Review Study Protocol	**X**	**X**
Sign ICF		**X**
Allodynia Symptom Checklist		**X**
DERS		**X**
PCS		**X**
GAD-7		**X**
PHQ-9		**X**
Mindfulness, FFM		**X**
PSS		**X**
Herth Hope Index		**X**
Life Orientation Test		**X**
Social Connectiveness Scale		**X**
Flourishing Scale		**X**
Brief Resilience Scale		**X**
NIH-Promis Measures of Sleep Disturbance		**X**
NIH-Promis Measures of Global Health (first question only)		**X**
Pittsburgh Sleep Quality Index		**X**
QST Measurements		**X**
Pain Threshold Testing		**X**
Vitals		**X**

QST – Quantitative Sensory Testing

Table 8: Summary of Schedule of Evaluations-Part II

Assessment	Telephone Screen	Screening/ Baseline Visit	Phone Call post 4 week baseline Headache log	Initial F/U	3mo follow-up	6 mo follow-up
Inclusion/Exclusion Criteria	X	X				
Enrollment		X				
Vitals		X		**X**	**X**	**X**
Teach use of REDCap		X				

Informed Consent Form		X				
Randomization			X			
Sociodemographic information		X				
Neurology Evaluation		X				
Headache Log		Begin	Continue	Continue	Continue	Continue
QST Heat Pain Assessments		X		X	X	X
INSTRUMENTS		X		X	X	X
Mindfulness-FFM		X		X	X	X
Emotion Regulation-DERS		X		X	X	X
Pain Catastrophizing-PCS		X		X	X	X
Pain Acceptance-CPAQ		X		X	X	X
Headache-related Disability -HIT-6		X		X	X	X
Headache-related Disability -MIDAS-one month		X		X	X	X
HA Management Self – Efficacy		X		X	X	X
Quality of Life-MSQOL, V.21		X		X	X	X
Perceived Stress-PSS-10		X		X	X	X
Depression-PHQ-9		X		X	X	X
Anxiety-GAD-7		X		X	X	X
Hope-Herth Hope Index (HHI)		X		X	X	X
Optimisim-Life Orientation Test-revised (LOT-R)		X		X	X	X
NIH PROMIS Sleep Disturbance		X		X	X	X
NIH PROMIS Global Health (first question only)		X		X	X	X
Pittsburgh Sleep Quality Index		X		X	X	X
Social Connectedness Scale – Revised		X		X	X	X
Flourishing Scale		X		X	X	X
Brief Resilience Scale		X		X	X	X
Credibility/Expectation Questionnaire		X		After 2nd class		

Working Alliance Inventory			After second class	X		
Client Satisfaction Questionnaire				X		
Patient Exit Interview-for Patient Centered Communication Skills			At end of each 8 week class	X		
Class Attendance			During 8 week class			
Home Practice			Begin with 1st class	Continue	Continue	Continue
Qualitative Interview				X		
Adverse Events			Begin with 1st class	Continue	Continue	Continue
Allodynia Symptom Checklist		X		X	X	X

FFM-Five Factor Mindfulness Scale
DERS-Difficulty in Emotion Regulation
PCS-Pain Catastrophizing Scale
CPAQ-Chronic Pain Acceptance Questionnaire
HIT-6: Headache Impact Test-6
MIDAS-Migraine Disability Assessment-one month
MSQOL-Migraine Specific Quality of Life, version 2.1
PSS-10-Perceived Stress Scale 10
PHQ-9: Patient Health-related Questionnaire-depression module 9
GAD-7: Generalized Anxiety Disorder 7

Description of Evaluations

Telephone Screen:
A study investigator will contact interested participants for a pre-screening telephone interview. At the beginning of the phone call, potential subjects will be informed of the nature and sensitivity of the questions, asked whether this is an appropriate time for them to answer these questions, and told how long the phone call is expected to take. Participants will be offered the option of completing the pre-screening in person, if they wish and if it is feasible. The pre-screening telephone interview will be performed to explain the protocol, determine eligibility, discuss informed consent, and answer questions. If eligible, they will then be offered participation. Those interested and eligible will be either immediately scheduled for a screening visit or will be called in the future to set it up. A letter will then be sent to them, with the consent form attached for review ahead of time if they would like, in advance of their study visit.

Baseline Visit:
The study staff will:

A-Consent Participants-Consenting procedures:
We will obtain consent before the experiment begins. At the onset of the study visit, participants will be provided informed consent by the PI or a qualified study team member. The consenting process will occur in a private clinic room. Subjects will be given time to ask questions and can discuss with family members. The consent form states the title and purpose of the study, an estimate of how many people may enroll, the duration of participation, the procedures that will be followed, any reasonably foreseeable risks or discomforts, and benefits to the participants or others that may be expected from the research. Information is provided about the disclosure and confidentiality of protected health information they will provide, that there is no cost to participants in the study, who sponsors the study, what happens if they experience an injury or illness as a result of participating, and whom to call if they have a question or problem. Participants will be informed of payment ($80 for completion of the study; $10 after the screening visit; $15 after the initial follow-up visit; $20 after the 3 month follow-up visit; and $35 after the 6 month follow-up visit). The telephone number of the Chairman of the Institutional Review Board will also be included for questions regarding rights as research subjects. The consent form will be signed and dated by the participant and by the person obtaining consent. We have obtained IRB approval for the study and the informed consent documents (Wake Forest IRB protocol # IRB00027845).

B-Neurology evaluation to confirm migraine diagnosis with history/neurological exam. Neurology evaluation will include vital signs, detailed headache and medical history, neurological exam (will include Structured Diagnostic Interview for Headache), and general physical exam. If participants have a headache at the time of the study visit, they will be rescheduled for a time when headache-free.

C-Complete baseline sociodemographic information and complete full set of instruments (See Schedule of assessments for full listing of all instruments)

D- Experimental Session of Quantitative Sensory Testing (QST) Measurements:
Thermal Probe: MEDOC TSA-II will deliver thermal stimuli with a 16 x 16 mm thermal probe. All temperatures will be < 50°C and no stimulus as designed produces tissue damage. We have significant experience using this technique and probe with no adverse events (Coghill's lab on > 750 subjects).

Psychophysical Training: To gain experience rating pain, subjects will be familiarized with 32, 5-second duration stimuli (35 to 49°C) with the Visual Analogue Scale (VAS), a 15 cm plastic sliding scale used to quantify pain sensation intensity and degree of

unpleasantness.[37] The VAS is an ideal pain measurement scale because of its ratio scale properties combined with its ease of administration and scoring.[38] The minimum rating is "no pain sensation" or "not all unpleasant" whereas the maximum is designated as "most intense imaginable" or "most unpleasant imaginable." The training will be conducted on the left arm, a location away from increased sensitivity/allodynia of head/neck regions often seen in patients with migraines.

Pain Threshold Assessment: The temperature of the probe will begin at 32°C and will increase at a rate of 0.5°C per second. The subject will be instructed to verbally respond when he or she first detects a sensation of pain. The thermode will return to baseline once the button is pressed. This will be performed up to four times, and the heat pain threshold will be determined as the average of the temperatures at which the stimulus was first perceived as painful (Yarnitsky and Sprecher, 1994). Stimulus temperatures employed for pain threshold testing will not exceed 50°C. This will be conducted on the right arm.

Experimental Session: We will administer the noxious thermal stimulation on the right calf by starting at 35°C and increasing with a 6°C rise/fall rate with a 5 second plateau up to the randomly administered temperatures of 43, 45, 47, and 49°C. Each temperature will be repeated x 3 and delivered pseudorandomly. To minimize sensitization, habituation, and hyperalgesia, all trials will be separated by 30 seconds and systematically distributed over the calf to minimize repetitive stimulation of the same skin site.[1,37,39] Perception of intensity and unpleasantness will be measured with the VAS scale after each temperature. Each series will be repeated twice. Dr. Wells has been trained in the performance and analysis of QST measurements.

The specified arm/leg positioning of the probe may be adjusted if needed.

E-Headache Logs-Participants will be taught by study staff how to capture daily migraine information using REDCap electronic data capture tools (or iPod touches for those without internet access). Headache logs will capture migraine day, duration, severity (pain intensity and pain unpleasantness), medications used for treatment, associated symptoms (nausea, vomiting, photophobia, phonophobia, osmophobia)

Randomization:
After the baseline evaluation, participants will track migraines x 4 weeks to 1) confirm diagnosis; 2) confirm ability to log daily; and 3) use as the 4 week "pre-trial" baseline migraine data. Once 4-week migraine logs are reviewed by study staff to ensure eligibility, participants will be randomized 1:1 to either MBSR or the control group, stratified by migraine frequency (low frequency of 4-9 headaches/month or high frequency of 10-20 headaches/month).. Treatment assignments will be generated by a permuted blocks method with randomly varying block size and sealed in numbered, opaque envelopes. Dr. Houle will generate the randomization (using SAS program "PROC PLAN" statement). Participants in both groups will continue to track their migraines with their daily REDCap logs for the duration of the trial. The PI will be blinded to the randomization groups.

Selection Bias, Blinding and Expectations: Recruitment materials and consents will state we are studying "better ways to manage migraines" without describing meditation or yoga. This approach will serve three purposes: 1) participants will be blinded to the active intervention; 2) we will avoid having participants who are only interested in MBSR, which could cause selection bias and increase the risk of control group dropouts; 3) this will minimize differences in expectations (which we will also measure) based on group assignment.

Expectations will be measured using Credibility/Expectancy Questionnaire[96] at the baseline visit AND after the 2nd class session.

Therapeutic Alliance: The two interventions require instructors with different expertise and cannot be the same person. However, the quality of the therapeutic relationship between participant and instructor will be measured after the interventions (at the initial follow-up) using the 12 item Working Alliance Inventory.

Treatment Fidelity: In addition to having the same instructor for each group lead all cohorts, we will implement a detailed treatment fidelity plan to monitor and ensure that the design, delivery, and receipt of both interventions are completed as intended (see Table 7).[97,98] We will also assess satisfaction with the programs with the Client Satisfaction Questionnaire[99] at the initial follow-up.

Table 7: Assessment of Treatment Fidelity

Aspect of Treatment Fidelity	Way to Ensure Fidelity is Accomplished	Further details
Study Design	Both intervention and control groups will receive the same "dose" of 8 weekly 2.5 hour classes, plus one "retreat" day, and may have daily homework of 30-45 minutes/day	
	Both instructors will follow detailed manuals for conducting their intervention	MBSR intervention will be conducted according to standard MBSR protocol
Provider Training	MBSR instructor is certified in teaching MBSR, has taught over 25 MBSR courses	Headache education provider is a neurologist with headache expertise
Treatment Delivery	Both instructors will be audiotaped during their sessions and 10% of randomly selected audiotapes will be reviewed to confirm treatment delivered as intended using checklists of required elements for each intervention and with evaluations of instructor's communication style; feedback will be provided if any deviations from expectations	
	Both instructors will have a standard expected check-list of both critical and minimal intervention components for each session's goals/requirements and will complete it at the end of each session	
	Participants will complete Patient Exit Interview to assess Patient Centered Communication Styles[100] of each group leader at the end of each session; participants will complete and place in sealed envelope so participant confidentiality maintained and instructor will not have access	The 2 instructors have been chosen specifically with similar interpersonal skills and levels of compassion with patient interactions
	Qualitative Interviews will further assess participants' perceptions of instructors' warmth and credibility	
Treatment Receipt	Class attendance will be monitored	

Enactment of Treatment skills	Participants will keep a daily log to track home activities if assigned	
	Qualitative interviews will also capture how individuals used/applied skills in their daily lives	

FOLLOW-UP VISITS
Follow-up visits will occur immediately after the 8 week class is over, 3 months later and 6 months later. At each follow-up visit, participants will complete the entire instrument assessment and the QST measurements. In addition, at the first follow-up visit, participants will complete a qualitative interview.

Qualitative Interviews: At the initial follow-up, a 30-minute semi-structured interview will be conducted with participants to further explore areas not captured in our standardized quantitative measures. This will be especially important in capturing measures of treatment fidelity not already captured, especially in capturing patient/instructor interactions and enactment of treatment skills.

Reporting Procedures

Plans for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects. Dr. Wells is a trained clinician and will oversee the interventions. If a medical emergency arises the appropriate steps will be taken to contact emergency services. At each study visit, the PHQ-9 survey will be scored immediately after completion by the participant. If the participant's responses suggest severe clinical depression, Dr. Wells will recommend that the participant see their primary care physician for treatment. If the participant's responses suggest active suicidal ideation, he or she will be sent directly to the emergency department.

We will promptly report any unanticipated problems, serious and unexpected adverse events, deviations or protocol changes to the IRB and Data Safety and Monitoring Board (See Data Safety and Monitoring Board for more details).

Serious adverse events (SAEs) that are unanticipated, serious, and possibly related to the study intervention will be reported to the I-DSMB, Wake Forest School of Medicine IRB, and NCCIH in accordance with requirements.

Unexpected fatal or life-threatening AEs related to the intervention will be reported to the NCCIH Program Officer within 7 days. Other serious and unexpected AEs related to the intervention will be reported to the NCCIH Program Official within 15 days.

Anticipated or unrelated SAEs will be handled in a less urgent manner but will be reported to the I-DSMB, Wake Forest School of Medicine IRB, NCCIH, and other oversight organizations in accordance with their requirements. In the annual AE summary, the I-DSMB Report will state that they have reviewed all AE reports.

The WFSM Institutional Data & Safety Monitoring Board (I-DSMB) will monitor the study for purposes of evaluating participant safety and study integrity. The I-DSMB is a Dean-appointed, multi-disciplinary, standing committee that is available to provide independent oversight for human research studies conducted by WFSM or by WFSM-affiliated faculty investigators. The board will review the progress of and safety for the study as described above in Part I. The DSMB will meet to review safety data at least once annually while the study has active participants, even if the prespecified review targets, as specified above, have not been met.

There will be no fee for the independent monitoring of the study. All protocol deviations and adverse events will be promptly reported to the I-DSMB as well the IRB. See DSMB plan for more details. See Table 3 above for further details of reporting.

Risks to subjects are reasonable in relation to the anticipated benefits to subjects and others.
The risks in participating in this study are minimal and the benefits can be significant to those who experience migraines. We will learn how Mindfulness based stress reduction techniques can assist with migraine pain. This work can be instrumental in employing safe non-pharmacological interventions for migraine pain which may be particularly beneficial as the MBSR technique can be performed concurrently with medications and have few side effects and may play a role in reducing stress.

Potential Risks
Potential physical, psychological, social, legal or other risks, their likelihood of occurring, seriousness to participants.

Experimental Heat Pain Assessments: The quantitative sensory testing may cause brief pain, but all temperatures will be < 50°C and no stimulus as designed produces tissue damage.. The thermal probe used for this experiment, MEDOC TSA-II, will deliver thermal stimuli with a 16 x 16 mm thermal probe.

The subject can easily pull away from the device if the feeling is not tolerable. Dr. Coghill's laboratory staff are experts in conducting the heat-pain intervention and the temperature of the thermal heat probe will be monitored at all times. His lab has conducted this procedure on over 750 participants and no serious adverse events have been associated with this device.

Mindfulness Body Stress Reduction intervention/Headache Education Control Group: A risk to taking part in this study is the likelihood of receiving an intervention (that requires time and energy) that may not be effective in helping to treat migraines. The classes or other study-related procedures may cause some, all, or none of the side effects listed below.
<u>Most Likely</u>
Gentle stretching can cause muscle soreness if muscles have not been exercised in a long time. Sitting for extended periods of time can be uncomfortable. Chairs will be provided for comfort, and participants will be allowed to move as needed to relieve any discomfort.
<u>Less Likely</u>
With any activity, there is always a risk of injury. The instructor will advise the participants to avoid any posture that causes discomfort or pain. The instructor will be attuned to watching for any problems during each session.
<u>Rare</u>
There have been rare case reports of meditation or yoga causing a brief limited episode of psychiatric illness. However, most of these case reports are in individuals with a prior history of unstable psychiatric illness. There are no known reports of this occurring in anyone in an MBSR class. Having a history of unstable psychiatric illness is an exclusion criteria for participating in this project so therefore we have in place an extra precaution to not encounter this risk.

Description of alternative treatments and procedures. The alternative is to not participate in the study or to refer to the personal physician for standard treatment.

STATISTICAL CONSIDERATIONS

General Design Issues

To examine the hypotheses, we will again rely on mixed effects hierarchical regression models with a distribution and link function appropriate to the outcome (e.g., binomial distribution and logit link for daily migraine probability). These models will allow us to fully utilize all of the information (i.e., rather than simply calculating change scores) by conceptualizing each diary entry as nested within a diary phase (baseline 4 weeks prior to randomization, 8 weeks of treatment, and 3 and 6 months of follow-up), within a person (random effects), who is nested within a treatment group. Missing data will be scrutinized and we will utilize sensitivity analyses and/or multiple imputation as required. The models will be conducted as described below:
Hypothesis 2a: MBSR will decrease the primary outcome of migraine frequency compared to an education control group;
Hypothesis 2b: MBSR will differentially affect the secondary outcome of the affective component (pain unpleasantness) of experimental heat pain compared to the education control group.
Hypothesis 2c: MBSR will improve the secondary outcomes of mindfulness, emotion regulation, pain acceptance, pain catastrophizing, and headache-related disability compared to an education control group.
Hypothesis 3A: High levels of baseline pain catastrophizing and emotional reactivity scores and high baseline levels of pain unpleasantness for experimental pain will predict the primary outcome response (migraine frequency) to MBSR.
Hypothesis 3B: Changes in mindfulness after MBSR will be directly associated with improvements in migraine frequency.

Sample Size and Randomization

Sample Size Calculation: For hypothesis 2a, using effect sizes from our pilot trial,[58] and by analyzing the data with our mixed effects hierarchical regression models, 44 participants/group (n=88) will provide >90% power with α=0.05 to detect a difference of 1.3 migraine days/month over the course of the trial (used PASS design) (Hypothesis 2a). Hypothesis 2b has a similar power function as Part I of this study. For hypothesis 3: since hypothesis 3b is the most difficult to evaluate, this RCT is powered on this hypothesis. This calculation assumes a multivariable model examining linear changes with the four predictors (plus intercept and slope). A sample size of 88 participants will give us 80% power with effects as small as $R^2 \geq 6\%$ in the variance of the slopes; smaller predictors are unlikely to be clinically significant.[101]

Randomization: Once 4-week migraine logs are reviewed by study staff to ensure eligibility, participants will be randomized 1:1 to either MBSR or the education control group, stratified by migraine frequency (low frequency of 4-9 headaches/month or high frequency of 10-20 headaches/month).. Treatment assignments will be generated by a permuted blocks method with randomly varying block size and sealed in numbered, opaque envelopes. Dr. Houle will generate the randomization (using the statistical SAS program "PROC PLAN" statement) and deliver the envelopes to the PI. Participants in both groups will continue to track their migraines with their daily REDCap logs for the duration of the trial.

Definition of Populations

As done in prior behavioral headache research,[69] all participants who attend at least ONE class will be included in the intention-to-treat analyses. This is a modified "intent to treat" analysis that ensures exposure to the independent variable and is used and felt to be very important by behavioral scientists.

Outcomes

Our primary outcome will be change in frequency of migraine days, defined as a calendar day (00:00 to 23:59)[102] when the patient reports 4 or more continuous hours of a moderate to severe headache (rating of 6-10 on 0-10 VAS pain intensity scale) and/or they treated a headache with abortive medication. Participants will track their headaches daily with REDCap logs to

demonstrate frequency, severity (both pain intensity and pain unpleasantness, as trained with QST), medications, and associated migraine symptoms (e.g., photophobia, phonophobia, nausea, vomiting). iPod Touch devices with Pendragon software will be available to those without internet access.

Secondary outcomes include changes in migraine severity (measured by pain intensity and unpleasantness on 0-10 VAS scale), migraine duration (hrs), frequency of headache days, headache duration, headache severity (measured by pain intensity and unpleasantness on 0-10 VAS scale), experimental heat pain intensity and unpleasantness (QST measurements), and changes in scores on validated measures of mindfulness, pain acceptance, pain catastrophizing, emotional reactivity, and headache-related disability compared to an education control group; determine factors that predict MBSR response on migraine pain. A headache day is defined as any day when a participant reports the presence of a headache.

We will also characterize participants before/after the intervention using measures of hope, optimism, quality of life, depression, anxiety, perceived stress, self-efficacy, sleep, fatigue, pain interference, satisfaction with participation in social roles, allodynia, and global health.

All the secondary outcomes and additional measures will be assessed with these standardized, reliable, well-validated instruments: Five-Facet Mindfulness Questionnaire (mindfulness),[57,103] DERS (emotion regulation),[3,104] PCS (pain catastrophizing),[2,36] Chronic Pain Acceptance Questionnaire (pain acceptance),[105] Herth Hope Index (hope),[106] Life Orientation Test-Revised (optimism),[107] Headache Impact Test-6 (HIT-6) (headache related disability),[108-110] Migraine Disability Assessment (MIDAS)-one month (headache related disability),[111,112] Patient Health Questionnaire-depression module, PHQ-9 (depression),[34] Generalized Anxiety Disorder-7, GAD-7 (anxiety),[35] Headache Management Self-Efficacy Scale (self-efficacy),[113] Migraine Specific Quality of Life Questionnaire, version 2.1 (MSQv2.1) (quality of life),[114,115] the Perceived Stress Scale 10, PSS (perceived stress), [116] the Brief Resilience Scale, the Resilience Scale for Adults, the Flourishing Scale, the Social Connectedness Scale-Revised (SCS-R), the PittsburghSleep Quality Index, the Allodynia Symptom Checklist (ASC-12), and well-validated NIH Patient Reported Outcomes Measurement Information System (PROMIS) measures of sleep, fatigue, pain interference, satisfaction with participation in social roles, and global health. Changes from baseline to initial follow-up will be primary outcomes; secondary outcomes will include changes from baseline to follow-ups at 3 and 6 months.

Additional Information Collected

Sociodemographic and clinical information will be collected at the screening visit.

Expectations for improvement: Expectations can impact results.[39,117] At baseline and after the second session, participants will rate their expectations using the Credibility/Expectancy Questionnaire.[96]

Class Attendance and Home Practice: Participants in both groups will track their home activities up to the 6-month follow-up visit via REDCap logs and the instructors will track patient class attendance.

Qualitative Interviews: At the initial follow-up, a 30-minute semi-structured interview will be conducted with participants to further explore areas not captured in our standardized quantitative measures.

Data Analyses

Analysis 2a: The probability that an individual experiences a migraine on any given day will be examined as a function of group (MBSR vs. control) and treatment phase. A statistically significant group x phase interaction will be interpreted as evidence that treatment differentially

impacted the daily probability of migraine. This effect size will be indexed by converting the daily probability to headache counts as recommended for clinical trials in headache.[118] If necessary we will model change using polynomial trajectories (i.e., growth curves) to better fit the time-course of treatment.
Analysis 2b: To examine this hypothesis, we will conduct an ANCOVA with pain unpleasantness at post-treatment as the dependent variable, group as the independent variable, and pain unpleasantness at pre-treatment as the covariate.
Analysis 2c: This analysis is identical to 2b, with the appropriate outcomes.
Analysis 3a: Baseline levels of pain catastrophizing and emotional reactivity will be used as predictors in the multilevel models predicting the trajectory of migraine attacks over the course of treatment.
Analyses 3b: This analysis is similar to 3a, except that changes in mindfulness (i.e., change scores from pre-treatment to post-treatment) will be used as predictor of migraine trajectory.

DATA COLLECTION AND QUALITY ASSURANCE

Data Collection Forms

Information will be collected from REDCap daily headache logs for appropriate diagnosis of migraines during an initial 4 week period prior to randomization and participants will continue to track daily headaches for the duration of the trial. Ipod touches with Pendragon software will be available to those without internet access and unable to use REDCap from home. Experimental heat measurements will be conducted at baseline and at each of the 3 follow-up evaluations. Participants will also complete standardized questionnaires using REDCap at baseline and at each of the 3 follow-up evaluations with an option to complete these questionnaires at home prior to the visit. In addition, a 30 minute qualitative interview will be conducted at the first follow-up visit to evaluate the participants' experience with the interventions. Each interview will be audiotaped. Socio-demographic and clinical information will also be collected at the screening visit.

Description of data that will be recorded on human subjects. Each 30 minute qualitative interview of the migraine and control subjects will be audiotaped and then transcribed. Participants will be photographed one of the study visits. These photos will be stored on the study's secure Ishare. Each subject will have provided informed consent to perform this.

Description of linkages to subjects and who will have access to subject identities. WFSM investigators and study staff will take measures to ensure the privacy and confidentiality of all study subjects. All participants will be assigned a study ID (unique ID) that will be used to link participant records and identify participants within the database. Only study investigators and the study team members will have access to the identity of participants.

Information about how specimens, records and data are collected; data collected specifically for research. All data are collected according to IRB approved study protocols specifically for research purposes. Specimens, records and data will be collected by study investigators, staff and physicians upon enrollment of the patients.

Quality Assurance

Protection Against Risk
Description of procedures for protecting against or minimizing potential risks, including risks to confidentiality, and assessment of likely effectiveness. All data collected will be completely confidential. Only investigators and their staff directly involved in this study will have access to the data. Records and forms will be kept in a locked file cabinet when not in use. No names will be stored on computer files for data analysis; no individuals will be identified in the results of this study. Access to computer-stored information will require knowledge of the data format, filename and password. Dr. Wells will use the results of this study for research only and

not include the results in a medical record. Any data that may be published in scientific journals will not reveal the subject's identity.

Plans for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects. Dr. Wells is a trained clinician and will oversee the interventions. If a medical emergency arises the appropriate steps will be taken to contact emergency services.

Institutional Review Board (IRB) Review

This protocol and the informed consent document have been approved by Wake Forest's IRB (Wake Forest IRB protocol # IRB00027845).

PUBLICATION OF RESEARCH FINDINGS

We plan to publish our findings in top-tier scientific, peer-reviewed journals.

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