# Study Protocol for Meditation Effects on Brain Function in Rheumatoid Arthritis

## NCT03975595

July 28, 2022

# JHM IRB - eForm A – Protocol

- **Use the section headings to write the JHM IRB eForm A, inserting the appropriate material in each. If a section is not applicable, leave heading in and insert N/A.**
- **When submitting JHM IRB eForm A (new or revised), enter the date submitted to the field at the top of JHM IRB eForm A.**

**********

## 1. Abstract

a. Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

The purpose of this study is to determine and optimize the neural mechanisms supporting mindfulness-based pain relief in rheumatoid arthritis (RA) patients. The scientific premise is that rheumatoid arthritis (RA) patients' use of an elemental mindfulness meditation practice—mindful breathing (MB)—and a positive emotion generative practice—savoring (SAV)—during noxious thermal stimulation will increase activation in the corticostriatal circuits. The corticostriatal circuits are attractive neural mechanisms of the putative benefits of mindfulness for RA because directly support cognitive appraisals of aversive stimuli and reward valuation, which are behavioral targets of our interventions. Target corticostriatal regions include the lateral orbitofrontal cortex (lOFC) and putamen, which support top-down control of attention and emotional appraisals, and the ventromedial prefrontal cortex (vmPFC) and nucleus accumbens (NAc), which support positive emotion regulation and reward appraisals. The behavioral output of the corticostriatal circuits is especially relevant for patients with RA, due to the flaring, unpredictable nature of RA pain and the importance of positive emotional function to RA pain coping. Our original plan was to randomize RA patients to a brief 4-session (20 minutes each) course of MB (n=20), SAV (n=20), or a sham MB control (n=20). To adjust to the ongoing COVID-19 pandemic, we will stop randomizing to MB and only randomize to SAV or sham MB. At post-intervention, participants will undergo functional MRI (fMRI) using a perfusion-based arterial spin labeling (ASL) technique during noxious thermal stimulation to determine if MB and SAV are associated with corticostriatal activation when compared to Sham MB.

## 2. Objectives (include all primary and secondary objectives)

1) Determine if MB activates corticostriatal circuits during noxious stimulation.
2) Determine if SAV activates corticostriatal circuits during noxious stimulation.
3) Determine if MB and/or SAV evidence stronger activation of corticostriatal circuits during noxious stimulation.

## 3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

RA is a chronic systemic inflammatory disorder that is characterized by variable levels of pain that range from mild to debilitating and can flare unpredictably. RA affects approximately 3 million individuals in the United States, accounting for an annual cost of 46.7 billion dollars.[1,2] Disease modifying anti-rheumatic drugs (DMARDs) are commonly used to manage RA symptoms by blocking pro-inflammatory cytokines, but symptom profiles and response to treatment vary substantially between patients[3]; up to 25%

of those receiving DMARDs show little or no improvement[4,5], and 20-40% of patients report chronic widespread pain that is poorly responsive to treatment.[6-8] Additionally, pain flares can be unpredictable, varying substantially within patients[9,10], even during the course of pharmacotherapy.[11-13] Given these considerations, there has long been a keen interest in the use of non-pharmacological treatments as an adjunct to traditional pharmacotherapy to help patients "self-manage" pain and other RA symptoms.[14-16] Indeed, research shows that modifiable psychological factors critically influence adaptation to RA.[17]

Mindfulness-based therapies are attractive candidate nonpharmacological interventions for the treatment of RA for several reasons. First, they attenuate the experience of acute pain at behavioral and corresponding neurobiological levels.[18,19] Second, they are premised on sustaining non-reactive attention to the breath in the present moment [20], and are therefore well-suited to promote acceptance-based appraisals of *real-time* internal and external experiences.[21] This type of skill is especially relevant to RA, given the flaring nature of RA pain.[12-14] Third, they are associated with reductions in anxiety and depression[22-24], which are common RA comorbidities that complicate treatment.[25,26]

A neural mechanisms approach to understanding the effects of mindfulness meditation in RA is appropriate because RA patients demonstrate central sensitization to calibrated noxious stimuli [27-29], and top-down cognitive and affective processes modulate the experience of RA pain.[30] Mechanisms for these central pain processes have not been identified in RA.[31] The striatum has dense inputs from the prefrontal cortex, midbrain, amygdala, and hippocampus, and its outputs are to the motor system and back to the cortex. These corticostriatal circuits are attractive as a candidate mechanism of chronic pain adaptation because of their role in evaluating sensory and affective stimuli, motivating actions in response to those stimuli, and promoting long-term learning that drives approach and/or avoidance of rewarding or aversive stimuli.[32-34] These core affective and behavioral outputs of the corticostriatal circuits are directly pertinent to how RA patients adapt to and cope with chronic pain, which often requires daily psychological adaptation to unpredictable pain flares.

Major Gap in Knowledge. Despite mindfulness meditation's promise as a treatment for chronic pain, and RA more specifically, there has been considerable methodological variability across studies, variable effect sizes, and a limited understanding of its mechanisms of action.[35-37] Furthermore, most mindfulness-based pain treatments are multicomponent packages mixing mindfulness meditation with other skills, such as yoga, group sharing/disclosure, and positive reappraisal.[38-42] In such multicomponent interventions, the unique variance in chronic pain outcomes accounted for by *mindfulness* is not clear.

We are aware of 5 published mindfulness-based randomized clinical trials (RCTs) that have included RA patients.[43-47] In general, they have shown benefits on subjective pain-related measures and general well-being.[43,46] But effects on pain severity and interference have been variable and objective markers of RA disease state, such as joint swelling and inflammation, have not changed.[43,46] Taken together, it is not clear how mindfulness confers pain-related benefits in RA.

Mindfulness meditation interventions have not generally yielded robust positive emotional responses[35], and some individuals actively downregulate positive emotions when practicing mindfulness.[48] This is unsurprising given that many mindfulness techniques encourage practitioners to avoid clinging to emotional states—negative or positive. However, the limited attention to positive emotion regulation in traditional mindfulness programs may miss an opportunity for intervention in chronically painful conditions like RA, as positive emotions acutely attenuate pain sensitivity[49-53] and promote adaptive coping with RA.[54-57] Specifically, longitudinal analyses have shown that within-person elevations in positive emotions weaken the relationship between flares in RA pain and negative emotions, suggesting that positive emotions alter RA patients' appraisals of pain.[56]

Despite the understanding that psychological features—particularly positive emotional function—directly influence RA outcomes[17], no study has examined neural mechanisms supporting the effects of mindfulness on RA chronic pain outcomes. **Without understanding the mechanisms by which specific mindfulness components work in RA, the population-level benefits of mindfulness interventions for patients with RA and other chronic pain conditions will likely be limited.**

How Proposed Work Will Fill the Gaps. The proposed project will address these gaps in two critical ways. First, we take a neural mechanisms approach to understanding how the employment of a single elemental mindfulness practice, MB, during noxious stimulation influences functioning of the lateral orbitofrontal cortex (lOFC) and putamen, two central nodes of the corticostriatal circuits involved in the top-down control of attention, emotions, and pain.[58,59] **We hypothesize that employment of MB during a noxious thermal stimulus will produce greater lOFC and putamen activation than a sham MB control.** These mechanisms have not previously been reported in patients with RA or any other pain disorder.

Second, we propose that SAV will engage different aspects of the corticostriatal circuits. SAV is traditionally a non-mindful cognitive strategy that promotes positive emotions through focused attention on pleasurable thoughts or sensory experiences.[60-62] Importantly, positive emotions are linked to activity within two other critical corticostriatal structures: the ventromedial prefrontal cortex (vmPFC), which is associated with the regulation of positive emotions[63-66], and the nucleus accumbens (NAc), which is associated with reward valuation in human and animal studies.[67-69] Indeed Speer et al.[70] showed that NAc and vmPFC function were significantly augmented during a basic savoring task, and NAc function correlated with the experience of positive emotions.

We plan to use these data to inform a follow-up study in which we combine MB and SAV and determine whether the combination optimizes the engagement of corticostriatal circuits during noxious stimulation.

## 4. Study Procedures

a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).

*Overview of Study*

We aim to demonstrate that MB promotes lOFC and putamen activation and SAV promotes NAc and vmPFC activation during noxious thermal stimulation among RA patients. We will execute a randomized controlled trial (RCT) comparing two arms: SAV, and sham MB in 40 RA patients (n = 20 per group). Originally, we also randomized participants to a third arm (MB). However, due to the disruption of the COVID-19 pandemic, we will no longer randomize to MB, in order to optimize our ability to complete the project on budget. The screening and intervention sessions will take place either via secure remote video conference (e.g., Zoom), or at Johns Hopkins Bayview Medical Center, as dictated by fluid laboratory density needs and participant safety precautions. There will also be a post-intervention fMRI task, which will take place at University of Maryland-Baltimore (UMB). The fMRI visit is the only that will take place at UMB.

In order to minimize the need for research-only in-person visits, telemedicine visits may be substituted for in person clinical trial visits or portions of clinical trial visits where determined to be appropriate and where determined by the investigator not to increase the participant's risks. As mentioned above, for this protocol, we will be able to move the informed consent, Baseline session and all 4 intervention sessions to remote/telemedicine.

Teleconsent will be used as opposed to in person consenting where possible to reduce unnecessary in person encounters specifically for a consent procedure. In the event teleconsent is utilized, the primary modality will be oral consent via RedCap. A REDCap oral consent will allow participants to review the consent at their leisure. Participants will have the option within the REDCap oral consent to note if they have any questions at each section of the consent. Participants are instructed to expect a response from the coordinator if they have any questions within any of these sections. An automated alert will trigger if the participant that they have a question within each section. Participants will have the option to download a blank copy of the IRB approved written consent as well as their completed copy of the REDCap version. A safegaurd has been implemented into the REDCap oral consent. The signature line will be hidden if the

participant does not answer the assessment of understanding questions correctly and an automated alert will be sent to the coordinator. Remote consenting in which the participant must return the signed copy of the consent is problematic since it may be weeks between the signing of the consent and their final visit at University of Maryland Baltimore. Participants who have a hearing impairment may still participate as they will be able to review the consent in REDCap and communicate with a coordinator via email. Participants who have a language impairment or non-English speakers will not be enrolled.

If oral consent via RedCap is not possible for any reason, participants will be provided with a copy of the Informed Consent prior to the teleconsent meeting either via email, fax, mail or previously provided during an in person visit. In events where a Physician/Mid-level provider consent signature is not required, the consent designee may proceed with teleconsent without an expectation for a follow-up in person consenting process. Participants will be given adequate time to consider the research study and ask questions prior to signing the consent form. Under this procedure, the consent designee must verify the participant physically signed the consent document either by viewing via video conference, obtaining a photo of the signed consent document; or obtaining verbal confirmation from the participant that he/she signed the consent form or agreed to participate electronically. The participant or LAR will sign and date/time the informed consent document. The document is then mailed, emailed or faxed to the consent designee. The participant will be asked to return the original signed document on their first in person visit. If the Informed Consent form is mailed to the consent designee by the participant the IRB-approved consent designee will sign the copy, which they possess after the participant has acknowledged signature on their copy. Once the original is received by the consent designee the copies will be attached to make a single document. In all other instances, once received, the IRB-approved consent designee signs, dates/times the informed consent document.

Prior to initiating telemedicine for study visits, the study team will explain to the participant what a telemedicine visit entails and confirm that the study participant is in agreement and able to proceed with this method. Telemedicine acknowledgement will be obtained in accordance with the Guidance for Use of Telemedicine in Research. In the event telemedicine is not deemed feasible, the study visit will proceed as an in-person visit if it is feasible under COVID-19 related safety protocols at that time, and as determined by the PI. Telemedicine visits will be conducted using HIPAA compliant method approved by Johns Hopkins and within licensing restrictions (e.g., Zoom).

Recruitment. Individuals with physician-confirmed RA will be targeted in this study. Patients will be recruited via physician referral from the Johns Hopkins Arthritis Center, which is directed by Co-I Bingham, or via IRB-approved advertisements.

Screening and Randomization:

**Telephone Screen:** Participants will undergo an initial screen over the phone (or in person if they are initially identified in the Arthritis Center Clinic), prior to informed consent. Participants meeting initial screening criteria will be scheduled for a subsequent screening session.

**Screening Session (Session 1):** At the screening session (either remote or in person), participants will complete screening measures through REDCap and an interview with study staff. Participants will also be shown a video to familiarize themselves with noxious thermal stimuli.

Eligible participants will be randomized to MB, SAV, or Sham MB, and starting in July, 2020, participants will only be randomized to SAV or Sham MB. The female to male ratio in RA is approximately 2-3:1[71,72], and RA is diagnosed at a higher rate in White Americans compared to African Americans.[73] To ensure these differences are accounted for, we will test sex and race as covariates in analyses.

Intervention Visits: Intervention sessions for each randomized condition will be one-on-one with an interventionist. Sessions (4 total) will take place via secure remote video conference (e.g., Zoom) or in the Johns Hopkins Behavioral Medicine Research Lab (BMRL) as dictated by COVID-19 conditions, and will last 20-minutes. Intervention visits will be scheduled 2 per week, so that the entire intervention will be completed in 2 weeks.

Intervention Descriptions

MB. As previously described[18,19,74,75], a well-validated 4 session [20 min/session(s)] MB training regimen will be employed to teach patients to independently practice MB. We have developed this regimen to provide basic and simple instructions for the exclusive practice of MB in order to reduce confusion and variable neural responses that could arise from incorporating multiple meditative didactics during training and neuroimaging, respectively. Thus, we do not integrate other traditional mindfulness practices such as walking, eating, loving-kindness, or yoga meditation. The proposed MB training regimen is premised on sustaining attention on the breath (Shamatha).[76] Throughout, subjects are taught to focus on the breath sensations occurring at the nose, abdomen/chest, and to attend to the dynamic aspects of breath while practicing non-judgmental awareness of discursive thoughts, feelings and sensations (Insight/Vipassana).[77]

Sham MB. The main purpose of the sham-MB intervention is to lead subjects to believe that they are practicing mindfulness-based breathing without the specific instructions related to mindfully attending to the breath in a non-evaluative manner.[18,75] This regimen is designed so that the primary difference between the MB and sham-MB group's training is the MB group's explicit mindfulness-based instructions (e.g., mindful attention to the breath). Consistent with previous work[18,75], and the fact that sham MB is not inert, the sham-MB group will be told that they are randomly assigned to a meditation-based intervention. They will not be informed that the intervention is explicitly not mindfulness-based breathing. In each of the four training sessions (20m/s), subjects will be instructed to close their eyes, and to take a deep breath "as we sit here in meditation" every 2-3 minutes.[18,75] All other aspects of the sham-MB intervention (posture, intervention room, facilitator; time providing instructions) will be matched to the MB training regimen.

SAV. The SAV condition will comprise 4 sessions in which participants are trained in the practice of savoring a technique commonly used in non-mindfulness positive psychology interventions to promote positive emotions.[78,79] The goal of savoring is to identify objects or experiences that elicit positive emotions and to focus one's attention on the positive feeling. Over the course of 4 sessions, participants will be trained to savor a pleasant memory.

Translation of Intervention Skills to fMRI Task

Participants will be informed at the outset that they will employ intervention skills during the post-intervention fMRI challenge. Subjects will also lie supine and MRI scanner sounds will be introduced in the last 10 minutes of training sessions 3 and 4, consistent with our prior work.[18,19]

Post-Intervention fMRI Procedures: Scans will be performed at the University of Maryland, Baltimore campus as soon as possible following the final intervention visit. At this visit, women will be tested for pregnancy, and all participants will be tested for recreational drugs/opioids. *S*ubjects will also undergo a QST familiarization session at prior to the fMRI scan. During the familiarization session, subjects will be exposed to noxious thermal stimuli, delivered via Peltier thermode (Pathway, Medoc Inc.) to the volar forearm or leg, and trained on differentiating pain intensity ratings from pain unpleasantness ratings. The MRI scan will require approximately 75 minutes. A standard anatomical T1-weighted scan (MPRAGE, voxels=1mm isotropic) will be collected, followed by a resting state-functional connectivity scan. fMRI scans will use an arterial spin labeling sequence (ASL). ASL provides a quantifiable measurement of CBF (ml/100g tissue/min) that provides a better assessment of physiological noise and image quality control.[80,81]

This is done by normalizing ASL 4D data by mean intensity values and designating each individual's respective white matter value as a nuisance covariate in first-level analyses.[82,83] Heart and respiratory rate data will be collected during the scans for use in removing physiological noise from the fMRI data. There will be several runs of rest and several runs in which participants are instructed to practice the skill learned in their respective intervention (MB, SAV, or Sham MB). Thermal stimuli will be delivered by a Pathway (Medoc Inc.) thermal stimulator to the volar forearm or leg. Thermal stimulus blocks will be pseudorandomly interleaved in each set of the rest and "practice" runs so that runs will alternate between temperatures. A cue will precede each and participants will subsequently rate pain intensity and unpleasantness using a visual analog scale.

For the "rest" runs, subjects will be asked to not move and direct their eyes to a fixation cross. In MB and Sham MB runs, subjects will be asked direct their eyes to a fixation cross and "begin meditating and continue meditating until the end of the experiment." In the SAV runs, subjects will be asked to practice savoring a positive thought, emotion or memory. In all conditions, participants will be periodically asked to rate their subjective experience (e.g., pain intensity; pain unpleasantness; emotional state) while in the scanner. Following the fMRI procedures, participants will complete questionnaires assessing levels of positive and negative emotions, and the extent to which they experienced mindfulness and/or savoring during the scan.

**Questionnaires:**

*Screening Measures:*

Chronic Pain: The **Brief Pain Inventory** (BPI[32;146]), a widely-used, well-validated "generic" pain measure for assessing chronic nonmalignant pain that measures of pain severity and interference.[32;67;146] The Graded Chronic Pain Scale (GCPS)[84] is an 8 item inventory assessing pain severity and disability and the degree to which one is limited in one's activities by pain.

Health History: A **health history** questionnaire will be completed to assess general health and ensure no exclusionary criteria are exhibited. Several additional questionnaires will also be administered to evaluate pain-related characteristics. Current and past mental health will be assessed with the Mini Neuropsychiatric Interview (MINI).[85]

*Clinical Outcome Measures:*

Clinical Pain Intensity, : PROMIS Pain Intensity is a short form that measures the degree of pain "on average" over the past 7 days. It has been validated in RA patients by Co-I Bingham's group[86] and shown to have ecological validity.[87] We will use the short form included in the PROMIS-29A battery.

Clinical Pain interference: PROMIS Pain Interference[88] is a 41-item bank that assesses the degree to which pain negatively impacts functioning. It can be administered using computerized adaptive testing (CAT) and has been validated in RA patients.[86] Veehof et al.[36] note that pain interference has been under-assessed across mindfulness trials in pain populations and argue strongly in favor of including it as a primary endpoint. We will use the short form included in the PROMIS-29A battery.

Fatigue: PROMIS Fatigue is a 90 item bank that is available as a CAT or fixed length short forms.[89] It has been validated in an RA sample[86] and shown to have ecological validity.[87] We will use the short form included in the PROMIS-29A battery.

Disease Activity: The Clinical Disease Activity Index (CDAI)[90] is a composite clinical measure that includes a count of swollen joints (0-28), tender joints (0-28), a patient report of global disease activity (VAS 0-100) and a clinician report of global disease activity (VAS 0-100). This will only be administered under in-person conditions, and cannot be administered with participants who undergo remote baseline and intervention sessions.

*Other Secondary Measures and Covariates*

Mindfulness: The Five Facet Mindfulness Questionnaire (FFMQ)[91] has 39 items on the mindfulness factors of observing, describing, acting with awareness, nonjudgment, and nonreactivity.
Savoring: The Savoring Beliefs Inventory (SBI)[92] is a 14-item measure of one's perceptions about one's capacity to savor pleasant experiences in the past, present and future. It includes an 8-item subscale assessing perceived capacity to "savor the moment."
Positive and Negative Affect: The Positive and Negative Affect Schedule-X (PANAS-X)[93] is a 60-item measure assessing perceived intensity of various specific emotions, which are aggregated to form positive and negative affect scales, and series of subscales.
Depression and Anxiety: We will measure depressive and anxiety symptom severity using the PROMIS depression and anxiety items, respectively, and covary them in our analyses. We will use the short form included in the PROMIS-29A battery.
PROMIS-29A Battery: In addition to pain, pain interference, fatigue, depression and anxiety (described above), the PROMIS-29A Battery also assesses Ability to Participate in Social Roles and Activities, Physical Function, Sleep Disturbance, and Stiffness. We will administer the battery.
Self-Efficacy for Managing Symptoms: The PROMIS Self-Efficacy for Managing Symptoms (SEMS) CAT is based on a 28-item bank that includes assessment of the level of confidence to manage/control symptoms in different settings and to keep symptoms from interfering with work, sleep, relationships, or recreational activities. This has been recently validated in chronic conditions[94]. We will use the short form, which is separate from the PROMIS-29A battery.
Pain Catastrophizing Scale (PCS): The PCS[95] is a 13-item scale that assesses the degree to which individuals magnify, ruminate, and experience helplessness about pain.
Snaith-Hamilton Pleasure Scale (SHAPS): The SHAPS[96] is a 14-item measure assessing the degree to which individuals experience pleasure from common activities of daily living.
Pain Resilience Scale (PRS): The PRS[97] is a 14-item measure of resilience to pain that has been validated in the context of both experimental and clinical pain.
Nondual Awareness Dimensional Assessment (NADA): The NADA[98] includes a 13-item trait questionnaire and a 3-item state questionnaire that assess the extent to which an individual experiences self-transcendent states of consciousness.
Pain and Pleasure Body Map: The Pain and Pleasure Body Map[99] assesses areas across the body in which people endorse experiencing pleasurable or painful physiological sensations.
Meta-cognitive Processing Scale (MPS): The MPS[100] is a 20-item measure assessing ways in which individuals experience thoughts, emotions, and feelings.
Mindful Reinterpretations of Pain Scale (MRPS): The MRPS[101] is a 9-item scale used to evaluate the frequency with which individuals engage in cognitive reappraisals of pain.
Freiburg Mindfulness Inventory (FMI): The FMI[102] is a 14-item instrument that measures the perceived state of mindfulness, and is sensitive to change following intervention.
Treatment Expectancy and Perceived Treatment Effectiveness: We will ask participants to complete a visual analog scale assessing the magnitude of expectation that meditation will reduce pain. Additionally, we will ask participants to complete a separate visual analog scale assessing how effective they felt they were at meditating.
Short Suggestibility Scale (SSS): The SSS[103] is a 21-item questionnaire that assesses the general tendency to accept messages.
Insomnia Severity Index (ISI): The ISI[104] is a 7-item instrument that quantifies the perceived severity of insomnia symptoms.
Determinants of Meditation Practice Inventory-Revised (DMPI-R): The DMPI-R is a 12-item measure[105] assessing four domains of perceived barriers to meditation: Low Perceived Benefit, Perceived Inadequate Knowledge, Perceived Pragmatic Barriers and Perceived Sociocultural Conflict.

b. Study duration and number of study sessions required of research participants.

The study should last approximately 4-5 weeks, depending on participants' schedules and availability of the MRI scanner. There will be 6 sessions: 1 screening session; 4 intervention sessions; and 1 post-intervention fMRI challenge.

c. Blinding, including justification for blinding or not blinding the trial, if applicable.

Participants, assessment technicians, and investigators will be blind to treatment assignment, but the interventionist cannot be blinded. To standardize expectations across conditions, MB, Sham MB, and SAV will all be described in general terms to participants as "meditation-oriented" interventions. After completion of the study and/or if subjects remove themselves from the study, we will fully debrief subjects to the nature of the study. We will inform subjects that our main purpose was to compare mindfulness meditation, sham meditation, and savoring on pain sensitivity and the brain mechanisms involved in these techniques.

d. Justification of why participants will not receive routine care or will have current therapy stopped.

N/A

e. Justification for inclusion of a placebo or non-treatment group.

The Sham MB condition is needed to control for expectancy effects associated with MB and/or SAV.

f. Definition of treatment failure or participant removal criteria.

Subjects are free to withdraw from participation in the study at any time upon request, and the investigator may withdraw a subject from participation for any of the following reasons (subjects withdrawn after randomization will not be replaced):

- Withdrawal of consent.
- Subject noncompliance with the protocol that results in inability to assess primary outcomes.
- Initiation of any treatment or medication that might affect RA or the investigator's ability to assess study outcomes, as determined by the investigator.
- Any event, condition, or situation that would make continued participation in the study not in the best interest of the subject, as determined by the investigator.

g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

Those who wish will be offered a list of mindfulness-based practitioners and will be referred for care as appropriate.

## 5. Inclusion/Exclusion Criteria

*Inclusion Criteria.* 1) 30-70 year olds; 2) have a physician-confirmed diagnosis of RA.

*Exclusion Criteria.* 1) unstable medical or psychiatric morbidity within 3 months; 2) lifetime history of alcohol or substance use disorder; 3) current use of opioids (other than tramadol and/or codeine) for therapeutic or non-therapeutic purposes; 4) positive toxicology screen for recreational drugs; 5) pregnant or lactating women; 6) presence of any comorbid idiopathic (e.g., fibromyalgia) chronic pain condition; 7) prior meditation experience, with the exception of yoga; 8) cannot tolerate noxious thermal pain at any level above pain threshold; 9) contraindicated for MRI, assessed on an individual basis (e.g., metal devices, claustrophobia)

Plan for Medications. Current use of prescription opioids (other than tramadol and/or codeine) will be exclusionary because these medications directly influence corticostriatal circuits.[106-108] Fewer than 2% of RA patients in the Johns Hopkins Arthritis Center—the primary recruitment site—are currently prescribed

opioids based on recent chart review. To ensure feasibility and promote generalizability, RA patients prescribed other medications commonly used in pain management, including antidepressants or non-opioid analgesics (e.g. NSAIDs), *will* be included. To minimize the impact of those allowable medications on primary aims, we will 1) ensure that patients are on a stable dose (>4 weeks) before enrolling in the study and that doses are anticipated to remain stable over the course of the study (confirmed by Dr. Bingham); and 2) include medication classifiers as covariates.

**6. Drugs/ Substances/ Devices**

a. The rationale for choosing the drug and dose or for choosing the device to be used.

N/A

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

N/A

c. Justification and safety information if non-FDA approved drugs without an IND will be administered.

N/A

## 7. Study Statistics

a. Primary outcome variable.

Primary outcomes include brain function in the corticostriatal circuits.

b. Secondary outcome variables.

Secondary outcomes include experimental pain sensitivity, and RA clinical pain pain-related measures.

c. Statistical plan including sample size justification and interim data analysis.

Sample Size Estimation: The analysis plan outlined below includes simplistic models that ensure that we capture the main effects that we hypothesized. While more complex statistical models are plausible, the use of one- and two-sample t-tests allows us to confidently determine a sample size that achieves statistical power based on previous work. Notably, this study is not powered for efficacy or effectiveness, but rather to observe intervention group differences on activation of corticostriatal circuits.

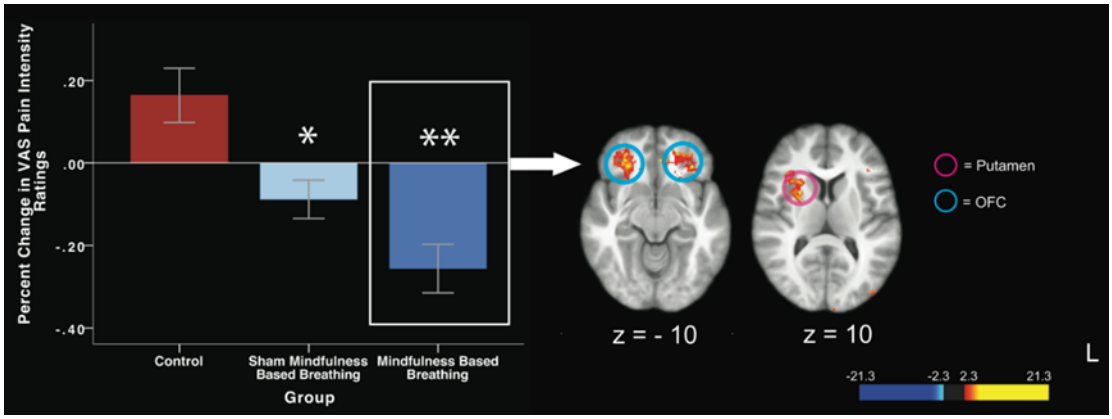


**Figure 1.** Left column: **The MB group significantly reduced pain ratings when compared to the sham-MB and control manipulations. *The sham-MB group significantly reduced pain ratings when compared to the control group. Right column: In the presence of noxious heat, mindfulness-based analgesia was associated with greater activation in the bilateral orbitofrontal cortex (OFC) and right putamen.

Zeidan and colleagues have repeatedly demonstrated[18,19] that sample sizes ≥ 15 (per group) reliably detect the neural mechanisms supporting meditation-induced analgesia in both between and within-person designs. To more specifically power the study, we ran a preliminary analysis from a colleague's data set (Dr. Fadel Zeidan) and examined subjects' behavioral and neural (arterial spin labeling fMRI) pain responses before and after each group's respective interventions (MB vs. sham). As shown in Figure 1, while both sham MB and MB reduced pain, they did so via distinct brain mechanisms: MB-based analgesia was associated with greater activation in the bilateral OFC and right putamen[18]. We used a neuroimaging-based power calculation software (Neuropowertools) and entered the contrast of parameter estimates from the preliminary analysis in Figure 1. Our simulation indicated that n=17/group will provide over 80% power to test the hypotheses that interventions have differential effects on corticostriatal activation during noxious thermal stimulation, correcting for multiple comparisons. To account for loss of degrees of freedom due to random cluster effects associated with the randomization, we will target n=20/group (N=40 total) for the R61 phase.

Data Analysis: fMRI data preprocessing will be performed using methods previously described in our work.[18,19] Briefly, ASL images will be combined into a single CBF volume, and motion will be corrected using filters designed to minimize perfusion-based fluctuations. After these corrections are performed, global CBF will be calculated as a voxel-wise mean from the CBF volume. All non-fMRI variables will be checked for normality, and any non-normal outcome measures will be log-transformed as appropriate. Sex is an important biological variable in chronic pain[109], and we will report data disaggregated by sex.

However, due to the overrepresentation of females in RA, we are not powered to test for sex differences. In addition, a priori covariates will include sex, race, medication classifiers, age, clinical pain severity, depression symptoms, and anxiety symptoms, as each has been linked to variation in RA symptoms and other rheumatic diseases.[26,110,111] Missing data will be handled by restricted maximum likelihood. If the missing-at—random assumption is violated, multiple imputation will be considered. Two-tailed p values ($\alpha = .05$) with 95% confidence intervals will be used to evaluate statistical significance.

The functional image analysis package FSL (FMRIB Software Library, Oxford, UK) will be used for first and second level statistical analyses. Functional images derived from CBF volumes are concatenated into a 4D volume for each individual, smoothed, normalized, and coregistered onto structural images using a standard nonlinear transformation.[112,113] Next, regional signal changes in a priori regions (lOFC, putamen, vmPFC, and NAc) are assessed in first level, with T/F statistic images Gaussianized and cluster thresholded to correct for multiple comparisons across brain voxels.[114]

Mixed effects modeling will be used as the primary analytic strategy for the primary outcomes. In our group therapy RCT design, mixed effects models permit the modeling of cohort-level random effects, as well as heterogeneous variance/covariance matrices to account for potential alpha inflation due to cohort-level clustering. We will test regional signal change in each ROI using mixed effects models examining within-person main effects of thermal stimulus (HEAT; i.e., painful vs. warm) and skill practice (PRACTICE; i.e., rest vs. active practice in the scanner during delivery of thermal stimuli), and the between-person main effect of intervention condition (CONDITION; i.e., MB vs. Sham MB vs. SAV), as well as their requisite 2-way and 3-way interactions. Thus, the HEAT X PRACTICE X CONDITION interaction will test the extent to which CBF in each a priori corticostriatal region varies during the active practice of either Sham MB, or SAV, relative to rest. Planned comparisons will test each of the HEAT X PRACTICE 2-way interactions within intervention groups to aid in the interpretation of the 3-way interaction.

## Updated Statistical Approach due to Covid-19

*Due to COVID-19 restrictions, we had to drop one arm from the study (Mindful Breathing). As such, a new statistical analysis plan was developed that we detail in the next section.*

**fMRI Pre-Processing:** Imaging analysis was conducted using Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (Center for FMRIB, University of Oxford, Oxford, UK) and ASL data processing toolbox. Five subjects were excluded from analysis due to detected image artifact or excessive motion. A total of 29 subjects (15 SAV group, 14 NMB) were included in the final imaging analysis. Subjects underwent 8 functional (ASL) runs during the MRI challenge session. The 8 ASL images that resulted from the runs represented combinations of two experimental conditions: Pain (nonpainful warm stimulus vs. noxious heat) and Practice (no meditation vs. meditation). These combinations occurred in the following order: 1. warm + no meditation; 2. noxious + no meditation; 3. warm + no meditation; 4. noxious + no meditation; 5. warm + meditation; 6. noxious + meditation; 7. warm + meditation; 8. noxious + meditation.

ASL images were motion corrected using the ASL MRI MoCo Method (Wang 2012). An additional motion correction and signal outlier filtering step was included (Tan et al 2009) to account for excessive motion and corruptive signal fluctuations. ASL images were converted into absolute CBF units according to the general kinetic model. The 8 CBF images were concatenated, intensity normalized, and then smoothed with a 9mm full-width half maximum (FWHM) Gaussian kernel. The images were spatially normalized to the MNI (Montreal Neurologic Institute) standard space using a 12-parameter affine transformation and then a nonlinear transformation. Additionally, a global white matter value was calculated for each CBF image by

extracting average white matter values from FSL's MNI152 white matter mask. The global white matter value was included in statistical models as a nuisance regressor.

**Statistical Approach for fMRI:** A group one-sample t-test (n = 29) was used to determine whole-brain, pain-related regions. The two Warm+No Meditation scans were subtracted from the two Noxious+No Meditation scans and then averaged. This average residual value per subject was used as the dependent measure included in the one-sample t-test.

Multiple regression analyses investigated the relationship between pain intensity/unpleasantness ratings and CBF during the Noxious condition. The 1st regressor consisted of the mean difference between the 2 Noxious+no Meditation scans vs Noxious+Meditation scans. The 2nd regressor included the percent change in subjects' pain intensity ratings from the Noxious+no Meditation to the Noxious+Meditation scans. The 3rd regressor included the percent change in the subjects' pain unpleasantness ratings from the Noxious+no Meditation to the Noxious+Meditation scans. All 3 regressors were orthogonalized to each other.

Because this was a proof-of-concept pilot mechanistic trial with a limited sample size, we set voxelwise threshold to 2.3, cluster corrected at p=0.05 (Worsley et al., 1992), in line with previous meditation-based imaging studies of similar size (Zeidan et al., 2015).

d. Early stopping rules.

We will report all adverse events and evaluate on a case-by-case basis whether the occurrence of a particular adverse event has implications for discontinuing the study to ensure participant safety and well-being.

**8. Risks**

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

*Interventions.* ***Mindful breathing (MB)*** is a basic mindfulness practice centered on maintaining non-reactive attention to breath in the present moment. Participants will be instructed to focus on breath sensations and practice non-judgmental awareness of disruptive internal milieu. No other mindfulness strategies will be instructed (e.g., loving kindness, yoga). ***Savoring (SAV)*** is a positive psychology practice designed to elicit positive emotions through attentional focus on a positive emotional experience. The proposed study will use a protocol adapted from Seligman et al.'s prior positive psychology interventions.[115] No mindfulness strategies will be instructed (e.g., focused breathing, non-judgmental awareness of disruptive thoughts). ***Sham MB*** will be used as a control intervention based on protocols from previous research. Specifically, participants will be instructed to close their eyes and take a deep breath every 2-3 minutes while meditating. Individuals' posture, the intervention room, facilitator, and time spent providing instructions will be consistent with the MB condition.

Associated Risks. ***MB, Sham MB, and SAV:*** Mild risks are associated with MB, Sham MB, and SAV. First, participants might experience increased somatic focus, which may initially cause heightened attention to clinical pain sensations that are very likely to resolve with distraction. Further, there is a slight chance that participants will experience increased frustration during initial training sessions while trying to maintain focus on breath sensations and/or positive emotional memories.

*Quantitative Sensory Testing (QST).* QST is a non-invasive, systematic method of measuring individuals' pain sensitivity using a variety of noxious stimuli (e.g., thermal, mechanical, cold pressor).

Associated Risks. Participants will likely find the QST procedures uncomfortable during administration of stimuli for a brief period of time. This effect is expected to be transient and to produce only mild levels of discomfort. There is a slight risk that sensitive individuals may experience temporary redness to the stimulated location on the skin.

*MRI:* During the MRI scan, participants will be exposed to a strong magnetic field. No long-term negative side effects have been observed from this type of study. However, the MRI equipment is very noisy, and participants will be given earplugs to reduce this effect. Being in an MRI scanner can cause claustrophobia in some people. For some people, MRI may be unsafe.

*Questionnaires.* Broadly, questionnaires will measure domains of emotional functioning, clinical pain severity, clinical pain interference, fatigue, and adeptness with mindfulness skills.

Associated Risks. A minor risk associated with completing questionnaires is that participants may become fatigued or bored. There is a slight risk that questions involving mental health might lead to increased emotional distress in sensitive participants.

*Urine Sample:* A urine sample will be collected at the screening phase of each study visit to exclude individuals who screen positively for pregnancy or recreational drug use.

Associated Risks. There are no known risks to collecting a urine sample. However, participants may feel psychological stress or anxiety due to the outcome of tests, such as if urine pregnancy test is positive.

Collection of Private Identifiable Information. All data as described above will be de-identified with private identifying information located in a separate, protected file. The private identifiable information that we will collect includes specific diagnostic verification from medical record review, birth date, and contact information.

Associated Risks. As in all human subjects protocols, there is a mild risk of breach of confidentiality of private identifiable information, which could inadvertently cause distress to the individual participant.

b. Steps taken to minimize the risks.

Planned Strategies for Minimizing Potential Risks. All research personnel will be fully trained in the protection of human subjects as required by the Johns Hopkins School of Medicine. Any modification to the protocol, consent form, or study forms will be submitted to the Johns Hopkns IRB for review. If any participant is in need of emergent medical or mental health care, we will escort the participant directly to the emergency room, located within 50 yards of our lab. Participants will be informed of all study risks during the informed consent process. We will ensure that participants are aware of their right to stop any procedure they find too uncomfortable. Specific protections against risks are outlined below.

*Interventions.* The PI is a licensed clinical psychologist and will be available to meet with any interested participant who experiences emotional or somatic discomfort, or excessive frustration, during the interventions.

*Quantitative Sensory Testing (QST).* First, participants will be informed of the QST procedure during the informed consent and will be able to make an informed decision regarding their study participation. Second, we will use standardized QST procedures with which we have extensive experience, and that are known to produce transient effects that are unlikely to produce any residual pain. Third, the equipment used for thermal stimuli has an upper limit (51°C) at which the system will automatically shut down to prevent tissue injury. Fourth, participants will be informed that they can revoke their consent to participate in the pain testing at any time without penalty. Fifth, the

participants will be monitored throughout the duration of their outpatient visits by study staff and will have access to medical care and concomitant medications to treat residual pain, if necessary. Finally, QST equipment is regularly tested to ensure proper functioning.

*MRI:* We will perform a preliminary screening before the participant is enrolled in the study to ensure there are no obvious contraindications for MRI, such as the presence of a pacemaker or claustrophobia. On the day of the MRI scan, before the participant undergoes MRI we will perform a standardized screening to ensure that it is safe for the participant to undergo MRI. In the event that participants become claustrophobic, they can press an emergency buzzer and we will remove them from the scanner. The scanner has an intercom system so we will always be in contact with the participants and they can request to be removed from the scanner.

*Questionnaires.* Participants will be offered breaks while completing questionnaires if fatigued or bored. Participants will also be instructed that they do not need to disclose any information that may be too uncomfortable and of their right to stop the questionnaire. If a participant experiences psychological distress related to completing questionnaires, a study clinical psychologist (licensed in the state of Maryland) will be available to intervene as necessary.

*Urine Sample:* Strict confidentiality of the sample and results will be maintained. Urine pregnancy testing results will be shared with participants. A licensed study clinical psychologist or the study physician will discuss any positive pregnancy test results directly with the participant and make appropriate referrals or recommendations for further medical care as warranted.

*Protection of Private Identifiable Information/Confidentiality.* Every effort will be made to prevent a breach of confidentiality. In accordance with HIPAA regulations, all potential participants will be fully informed of their rights pertaining to disclosure of patient health information. The data will be managed and protected as follows: (1) participants will be assigned a code number and only the code number will be used to identify the neuroimages (at UMB) and urine results, standardized questionnaire information, and QST data; (2) a unique, password-protected electronic file will be created for participants' protected health information and identification number that will be stored in a separate location on a secure server from study-specific data; (3) written documents concerning the studies will be kept in locked cabinets with the key maintained in a secure location within the research center; (4) data will be housed on secure workstations connected to servers behind either a JHU (behavioral data) or UMB (neuroimaging data) firewall that are accessible by study members who hold authenticated logins and passwords, and data will be backed up by the PI and HIPAA-trained research assistant regularly onto an encrypted hard drive. All personnel will have undergone training/certification for handling such materials as required by the NIH and Johns Hopkins University. Only summaries of group data, without any individual identification, will be reported in any publications or presentations.

c. Plan for reporting unanticipated problems or study deviations.

All adverse events will be reported to the IRB and other relevant agencies as required. The Principal Investigator and Co-investigators are responsible for reporting such events.

At each study visit, an electronic adverse event tracking form (e.g., in RedCap) will be used to record and track any emergent adverse events. A staff entry of an adverse event will trigger an email to the study team and alert the PI to review and complete the adverse event tracking form, grading the severity of the AE (1-mild, 2-moderate, 3-severe), and determining the relatedness of the event to the research study. This form is also used in identifying when the symptom resolves and logging actions taken. The form includes the definition of a "Serious Adverse Event (SAE)." Should the AE be determined to meet the criteria of a SAE, the SAE tracking form opens automatically to capture that information. These forms will be maintained during the entire course of participation.

The PI will review AE tracking forms for identification of whether an AE is an unanticipated problem based on OHRP criteria. To make this determination, we will follow the OHRP algorithm, which considers whether the event is unexpected in nature, severity, or frequency. We will also consider whether the event is rated as related or possibly related to the study. Based on this information the PI will determine whether the AE suggests that the research places subjects or others at a greater risk of physical or psychological harm than previously known or recognized. AEs determined to be an unanticipated problem will be reported as described below.

Adverse events meeting criteria as **serious adverse events (SAEs)** will be reported as soon as possible and within 48 hours to IRB. The AE tracking form will automatically alert all study team members of the occurrence of an adverse event. The PI is notified directly via email to complete the AE report to facilitate immediate determination of the severity of the adverse event and whether it meets the criteria of an SAE. An AE determined to be **an unanticipated problem**, but not meeting the definition of an SAE will be will be reported promptly to IRB according to established IRB guidelines. All AEs, regardless of whether they are "serious" or an "unanticipated problem," will be reported in summary form regularly at monthly intervals to the entire study team and to IRB annually at the time of continuing review. Adverse event forms will be housed electronically (e.g., in RedCap) with all related information for seamless tracking, reporting and follow up. The participant's name will not be attached to any data and all information related to the adverse event will be identified by participant number.

Similarly, all protocol deviations will be tracked in the study database. Protocol deviations will be categorized according to type (e.g. Missing data, study visit out of window, incomplete questionnaires, etc) and reviewed at bi-monthly project meetings. All protocol deviations will be reported annually to the IRB at time of continuing review.

d. Legal risks such as the risks that would be associated with breach of confidentiality.

Although there is always a small risk that confidentiality will be breached, we believe this risk to be very minimal with the current study.

e. Financial risks to the participants.

None.

## 9. Benefits

a. Description of the probable benefits for the participant and for society.

All participants will receive an intervention from which they may benefit, including the sham MB intervention, which is an active deep breathing intervention. The knowledge to be gained regarding the effects of mindfulness and savoring on pain-related brain function in RA will yield potential benefits to those who have RA, and to society as a whole.

## 10. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

Participants may earn up to $200 for completing all procedures in this study. The remuneration details are summarized in Table 1:

| **Table 1** | Payment |
|---|---|
| Screening Visit 1 | $25 |
| Intervention Completion Bonus | $50 |
| Post-Intervention fMRI Visit | $75 |
| Bonus for Completing all Assessments | $50 |
| TOTAL | $200 |

**11. Costs**

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

There are no costs to participants.

## References

1. Alamanos Y, Drosos AA. Epidemiology of adult rheumatoid arthritis. *Autoimmunity reviews* 2005; **4**(3): 130-6.
2. Ma VY, Chan L, Carruthers KJ. Incidence, prevalence, costs, and impact on disability of common conditions requiring rehabilitation in the United States: stroke, spinal cord injury, traumatic brain injury, multiple sclerosis, osteoarthritis, rheumatoid arthritis, limb loss, and back pain. *Arch Phys Med Rehabil* 2014; **95**(5): 986-95. e1.
3. Van de Putte L, Atkins C, Malaise M, et al. Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. *Ann Rheum Dis* 2004; **63**(5): 508-16.
4. Moreland LW, Baumgartner SW, Schiff MH, et al. Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)–Fc fusion protein. *N Engl J Med* 1997; **337**(3): 141-7.
5. Handel ML, Nguyen LQ, Lehmann TP. Inhibition Of Transcription Factors By Anti-Inflammatory And Anti-Rheumatic Drugs: Can Variability In Response Be Overcome? *Clin Exp Pharmacol Physiol* 2000; **27**(3): 139-44.
6. Wolfe F, Häuser W, Hassett AL, Katz RS, Walitt BT. The development of fibromyalgia–I: Examination of rates and predictors in patients with rheumatoid arthritis (RA). *PAIN*® 2011; **152**(2): 291-9.
7. Wolfe F, Cathey M, Kleinheksel S. Fibrositis (Fibromyalgia) in rheumatoid arthritis. *The Journal of rheumatology* 1984; **11**(6): 814-8.
8. Ranzolin A, Brenol JCT, Bredemeier M, et al. Association of concomitant fibromyalgia with worse disease activity score in 28 joints, health assessment questionnaire, and short form 36 scores in patients with rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2009; **61**(6): 794-800.
9. Affleck G, Urrows S, Tennen H, Higgins P. Daily coping with pain from rheumatoid arthritis: patterns and correlates. *Pain* 1992; **51**(2): 221-9.
10. Stone AA, Broderick JE, Porter LS, Kaell AT. The experience of rheumatoid arthritis pain and fatigue: examining momentary reports and correlates over one week. *Arthritis & Rheumatology* 1997; **10**(3): 185-93.
11. Bartlett SJ, Hewlett S, Bingham CO, et al. Identifying core domains to assess flare in rheumatoid arthritis: an OMERACT international patient and provider combined Delphi consensus. *Ann Rheum Dis* 2012: annrheumdis-2011-201201.
12. Alten R, Pohl C, Choy EH, et al. Developing a construct to evaluate flares in rheumatoid arthritis: a conceptual report of the OMERACT RA Flare Definition Working Group. *The Journal of Rheumatology* 2011; **38**(8): 1745-50.
13. Hewlett S, Sanderson T, May J, et al. 'I'm hurting, I want to kill myself': rheumatoid arthritis flare is more than a high joint count—an international patient perspective on flare where medical help is sought. *Rheumatology* 2011; **51**(1): 69-76.
14. Flurey CA, Morris M, Richards P, Hughes R, Hewlett S. It's like a juggling act: rheumatoid arthritis patient perspectives on daily life and flare while on current treatment regimes. *Rheumatology* 2013; **53**(4): 696-703.
15. Flurey CA, Morris M, Pollock J, Richards P, Hughes R, Hewlett S. A Q-methodology study of flare help-seeking behaviours and different experiences of daily life in rheumatoid arthritis. *BMC Musculoskelet Disord* 2014; **15**(1): 364.
16. Lorig KR, Mazonson PD, Holman HR. Evidence suggesting that health education for self-management in patients with chronic arthritis has sustained health benefits while reducing health care costs. *Arthritis & Rheumatology* 1993; **36**(4): 439-46.
17. Sturgeon JA, Finan PH, Zautra AJ. Affective disturbance in rheumatoid arthritis: psychological and disease-related pathways. *Nature Reviews Rheumatology* 2016; **12**(9): 532-42.
18. Zeidan F, Emerson NM, Farris SR, et al. Mindfulness Meditation-Based Pain Relief Employs Different Neural Mechanisms Than Placebo and Sham Mindfulness Meditation-Induced Analgesia. *J Neurosci* 2015; **35**(46): 15307-25.
19. Zeidan F, Martucci KT, Kraft RA, Gordon NS, McHaffie JG, Coghill RC. Brain mechanisms supporting the modulation of pain by mindfulness meditation. *J Neurosci* 2011; **31**(14): 5540-8.
20. Zeidan F, Vago DR. Mindfulness meditation-based pain relief: a mechanistic account. *Ann N Y Acad Sci* 2016; **1373**(1): 114-27.
21. Bishop SR, Lau M, Shapiro S, et al. Mindfulness: A proposed operational definition. *Clinical psychology: Science and practice* 2004; **11**(3): 230-41.
22. Evans S, Ferrando S, Findler M, Stowell C, Smart C, Haglin D. Mindfulness-based cognitive therapy for generalized anxiety disorder. *J Anxiety Disord* 2008; **22**(4): 716-21.
23. Hofmann SG, Sawyer AT, Witt AA, Oh D. The effect of mindfulness-based therapy on anxiety and depression: A meta-analytic review. *J Consult Clin Psychol* 2010; **78**(2): 169.
24. Goldin PR, Gross JJ. Effects of mindfulness-based stress reduction (MBSR) on emotion regulation in social anxiety disorder. *Emotion* 2010; **10**(1): 83.
25. Pincus T, Griffith J, Pearce S, Isenberg D. Prevalence of self-reported depression in patients with rheumatoid arthritis. *Rheumatology* 1996; **35**(9): 879-83.
26. Dickens C, McGowan L, Clark-Carter D, Creed F. Depression in rheumatoid arthritis: a systematic review of the literature with meta-analysis. *Psychosom Med* 2002; **64**(1): 52-60.
27. Lee YC, Bingham CO, Edwards RR, et al. Pain Sensitization is Associated with Disease Activity in Rheumatoid Arthritis Patients: A Cross-Sectional Study. *Arthritis Care Res (Hoboken)* 2017.
28. Morris VH, Cruwys SC, Kidd BL. Characterisation of capsaicin-induced mechanical hyperalgesia as a marker for altered nociceptive processing in patients with rheumatoid arthritis. *Pain* 1997; **71**(2): 179-86.

29. Wendler J, Hummel T, Reissinger M, et al. Patients with rheumatoid arthritis adapt differently to repetitive painful stimuli compared to healthy controls. *J Clin Neurosci* 2001; **8**(3): 272-7.
30. Sturgeon JA, Zautra AJ. State and trait pain catastrophizing and emotional health in rheumatoid arthritis. *Ann Behav Med* 2012; **45**(1): 69-77.
31. Meeus M, Vervisch S, De Clerck LS, Moorkens G, Hans G, Nijs J. Central sensitization in patients with rheumatoid arthritis: a systematic literature review. Semin Arthritis Rheum; 2012: Elsevier; 2012. p. 556-67.
32. Haber SN, Calzavara R. The cortico-basal ganglia integrative network: the role of the thalamus. *Brain Res Bull* 2009; **78**(2): 69-74.
33. Haber SN. Corticostriatal circuitry. *Dialogues Clin Neurosci* 2016; **18**(1): 7-21.
34. Haber SN, Knutson B. The reward circuit: linking primate anatomy and human imaging. *Neuropsychopharmacology* 2010; **35**(1): 4-26.
35. Goyal M, Singh S, Sibinga EM, et al. Meditation programs for psychological stress and well-being: a systematic review and meta-analysis. *JAMA internal medicine* 2014; **174**(3): 357-68.
36. Veehof M, Trompetter H, Bohlmeijer ET, Schreurs KMG. Acceptance-and mindfulness-based interventions for the treatment of chronic pain: a meta-analytic review. *Cogn Behav Ther* 2016; **45**(1): 5-31.
37. Hilton L, Hempel S, Ewing BA, et al. Mindfulness meditation for chronic pain: systematic review and meta-analysis. *Ann Behav Med* 2016; **51**(2): 199-213.
38. Kabat-Zinn J. An outpatient program in behavioral medicine for chronic pain patients based on the practice of mindfulness meditation: Theoretical considerations and preliminary results. *Gen Hosp Psychiatry* 1982; **4**(1): 33-47.
39. Morone NE, Greco CM, Moore CG, et al. A mind-body program for older adults with chronic low back pain: a randomized clinical trial. *JAMA internal medicine* 2016; **176**(3): 329-37.
40. Morone NE, Greco CM, Weiner DK. Mindfulness meditation for the treatment of chronic low back pain in older adults: a randomized controlled pilot study. *Pain* 2008; **134**(3): 310-9.
41. Cherkin DC, Sherman KJ, Balderson BH, et al. Effect of mindfulness-based stress reduction vs cognitive behavioral therapy or usual care on back pain and functional limitations in adults with chronic low back pain: a randomized clinical trial. *JAMA* 2016; **315**(12): 1240-9.
42. Garland EL, Manusov EG, Froeliger B, Kelly A, Williams JM, Howard MO. Mindfulness-oriented recovery enhancement for chronic pain and prescription opioid misuse: results from an early-stage randomized controlled trial. *J Consult Clin Psychol* 2014; **82**(3): 448.
43. Fogarty FA, Booth RJ, Gamble GD, Dalbeth N, Consedine NS. The effect of mindfulness-based stress reduction on disease activity in people with rheumatoid arthritis: a randomised controlled trial. *Ann Rheum Dis* 2015; **74**(2): 472-4.
44. Brown CA, Jones AK. Psychobiological correlates of improved mental health in patients with musculoskeletal pain after a mindfulness-based pain management program. *The Clinical journal of pain* 2013; **29**(3): 233-44.
45. Zangi HA, Mowinckel P, Finset A, et al. A mindfulness-based group intervention to reduce psychological distress and fatigue in patients with inflammatory rheumatic joint diseases: a randomised controlled trial. *Ann Rheum Dis* 2011: annrheumdis-2011-200351.
46. Zautra AJ, Davis MC, Reich JW, et al. Comparison of cognitive behavioral and mindfulness meditation interventions on adaptation to rheumatoid arthritis for patients with and without history of recurrent depression. *J Consult Clin Psychol* 2008; **76**(3): 408.
47. Pradhan EK, Baumgarten M, Langenberg P, et al. Effect of mindfulness-based stress reduction in rheumatoid arthritis patients. *Arthritis Care Res (Hoboken)* 2007; **57**(7): 1134-42.
48. Lalot F, Delplanque S, Sander D. Mindful regulation of positive emotions: a comparison with reappraisal and expressive suppression. *Front Psychol* 2014; **5**.
49. Roy M, Peretz I, Rainville P. Emotional valence contributes to music-induced analgesia. *Pain* 2008; **134**(1): 140-7.
50. Roy M, Piché M, Chen J-I, Peretz I, Rainville P. Cerebral and spinal modulation of pain by emotions. *Proceedings of the National Academy of Sciences* 2009; **106**(49): 20900-5.
51. Kenntner-Mabiala R, Pauli P. Affective modulation of brain potentials to painful and nonpainful stimuli. *Psychophysiology* 2005; **42**(5): 559-67.
52. Rhudy JL, Williams AE, McCabe KM, Russell JL, Maynard LJ. Emotional control of nociceptive reactions (ECON): do affective valence and arousal play a role? *Pain* 2008; **136**(3): 250-61.
53. Rhudy JL, Williams AE, McCabe KM, Rambo P. Affective modulation of nociception at spinal and supraspinal levels. *Psychophysiology* 2005; **42**(5): 579-87.
54. Mun CJ, Thummala K, Davis MC, Karoly P, Tennen H, Zautra AJ. Predictors and social consequences of daily pain expectancy among adults with chronic pain. *Pain* 2017; **158**(7): 1224-33.
55. Sturgeon JA, Zautra AJ. Psychological resilience, pain catastrophizing, and positive emotions: perspectives on comprehensive modeling of individual pain adaptation. *Current pain and headache reports* 2013; **17**(3): 1-9.
56. Strand EB, Zautra AJ, Thoresen M, Ødegård S, Uhlig T, Finset A. Positive affect as a factor of resilience in the pain—negative affect relationship in patients with rheumatoid arthritis. *J Psychosom Res* 2006; **60**(5): 477-84.
57. Zautra AJ, Johnson LM, Davis MC. Positive affect as a source of resilience for women in chronic pain. *J Consult Clin Psychol* 2005; **73**(2): 212.

58. Ochsner KN, Gross JJ. The cognitive control of emotion. *Trends Cogn Sci* 2005; **9**(5): 242-9.
59. Starr CJ, Sawaki L, Wittenberg GF, et al. The contribution of the putamen to sensory aspects of pain: insights from structural connectivity and brain lesions. *Brain* 2011; **134**(7): 1987-2004.
60. Quoidbach J, Berry EV, Hansenne M, Mikolajczak M. Positive emotion regulation and well-being: Comparing the impact of eight savoring and dampening strategies. *Pers Individ Dif* 2010; **49**(5): 368-73.
61. Bryant FB, Chadwick ED, Kluwe K. Understanding the processes that regulate positive emotional experience: Unsolved problems and future directions for theory and research on savoring. *International Journal of Wellbeing* 2011; **1**(1).
62. Bryant FB, Veroff J. Savoring: A new model of positive experience: Psychology Press; 2017.
63. Lindquist KA, Satpute AB, Wager TD, Weber J, Barrett LF. The brain basis of positive and negative affect: evidence from a meta-analysis of the human neuroimaging literature. *Cereb Cortex* 2015; **26**(5): 1910-22.
64. Roy M, Shohamy D, Wager TD. Ventromedial prefrontal-subcortical systems and the generation of affective meaning. *Trends Cogn Sci* 2012; **16**(3): 147-56.
65. Etkin A, Egner T, Kalisch R. Emotional processing in anterior cingulate and medial prefrontal cortex. *Trends Cogn Sci* 2011; **15**(2): 85-93.
66. Wager TD, Davidson ML, Hughes BL, Lindquist MA, Ochsner KN. Prefrontal-subcortical pathways mediating successful emotion regulation. *Neuron* 2008; **59**(6): 1037-50.
67. McClure SM, Laibson DI, Loewenstein G, Cohen JD. Separate neural systems value immediate and delayed monetary rewards. *Science* 2004; **306**(5695): 503-7.
68. Ikemoto S, Panksepp J. The role of nucleus accumbens dopamine in motivated behavior: a unifying interpretation with special reference to reward-seeking. *Brain Research Reviews* 1999; **31**(1): 6-41.
69. Knutson B, Adams CM, Fong GW, Hommer D. Anticipation of increasing monetary reward selectively recruits nucleus accumbens. *J Neurosci* 2001; **21**(16): RC159-RC.
70. Speer ME, Bhanji JP, Delgado MR. Savoring the past: positive memories evoke value representations in the striatum. *Neuron* 2014; **84**(4): 847-56.
71. Kvien TK, Uhlig T, ØdegÅrd S, Heiberg MS. Epidemiological aspects of rheumatoid arthritis. *Ann N Y Acad Sci* 2006; **1069**(1): 212-22.
72. Symmons D, Turner G, Webb R, et al. The prevalence of rheumatoid arthritis in the United Kingdom: new estimates for a new century. *Rheumatology* 2002; **41**(7): 793-800.
73. Barton J, Trupin L, Schillinger D, et al. Racial and ethnic disparities in disease activity and function among persons with rheumatoid arthritis from university-affiliated clinics. *Arthritis Care Res (Hoboken)* 2011; **63**(9): 1238-46.
74. Zeidan F, Johnson SK, Diamond BJ, David Z, Goolkasian P. Mindfulness meditation improves cognition: evidence of brief mental training. *Conscious Cogn* 2010; **19**(2): 597-605.
75. Zeidan F, Johnson SK, Gordon NS, Goolkasian P. Effects of brief and sham mindfulness meditation on mood and cardiovascular variables. *J Altern Complement Med* 2010; **16**(8): 867-73.
76. Wallace BA. The Attention Revolution: Unlocking the Power of the Focused Mind. Somerville: Wisdom Publications; 2006.
77. Goenka SN. The Art of Living: Vipassana Meditation. Onalaska, WA: Pariyatti Publishing; 1987.
78. Hausmann LR, Parks A, Youk AO, Kwoh CK. Reduction of bodily pain in response to an online positive activities intervention. *The Journal of Pain* 2014; **15**(5): 560-7.
79. Hausmann LR, Youk A, Kwoh CK, et al. Testing a positive psychological intervention for osteoarthritis. *Pain Med* 2017; **18**(10): 1908-20.
80. Luh WM, Wong EC, Bandettini PA, Hyde JS. QUIPSS II with thin-slice TI1 periodic saturation: a method for improving accuracy of quantitative perfusion imaging using pulsed arterial spin labeling. *Magn Reson Med* 1999; **41**(6): 1246-54.
81. Luh WM, Wong EC, Bandettini PA, Ward BD, Hyde JS. Comparison of simultaneously measured perfusion and BOLD signal increases during brain activation with T(1)-based tissue identification. *Magn Reson Med* 2000; **44**(1): 137-43.
82. Restom K, Behzadi Y, Liu TT. Physiological noise reduction for arterial spin labeling functional MRI. *Neuroimage* 2006; **31**(3): 1104-15.
83. Behzadi Y, Restom K, Liau J, Liu TT. A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. *Neuroimage* 2007; **37**(1): 90-101.
84. Von Korff M, Ormel J, Keefe FJ, Dworkin SF. Grading the severity of chronic pain. *Pain* 1992; **50**(2): 133-49.
85. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *The Journal of clinical psychiatry* 1998.
86. Bartlett SJ, Orbai A-M, Duncan T, et al. Reliability and validity of selected PROMIS measures in people with rheumatoid arthritis. *PLoS One* 2015; **10**(9): e0138543.
87. Stone AA, Broderick JE, Junghaenel DU, Schneider S, Schwartz JE. PROMIS fatigue, pain intensity, pain interference, pain behavior, physical function, depression, anxiety, and anger scales demonstrate ecological validity. *J Clin Epidemiol* 2016; **74**: 194-206.

88. Amtmann D, Cook KF, Jensen MP, et al. Development of a PROMIS item bank to measure pain interference. *Pain* 2010; **150**(1): 173-82.
89. Cella D, Riley W, Stone A, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005–2008. *J Clin Epidemiol* 2010; **63**(11): 1179-94.
90. Aletaha D, Smolen J. The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. *Clin Exp Rheumatol* 2005; **23**(5): S100.
91. Baer RA, Smith GT, Hopkins J, Krietemeyer J, Toney L. Using self-report assessment methods to explore facets of mindfulness. *Assessment* 2006; **13**(1): 27-45.
92. Bryant F. Savoring Beliefs Inventory (SBI): A scale for measuring beliefs about savouring. *Journal of mental health* 2003; **12**(2): 175-96.
93. Watson D, Clark LA. The PANAS-X: Manual for the positive and negative affect schedule-expanded form. 1999.
94. Gruber-Baldini AL, Velozo C, Romero S, Shulman LM. Validation of the PROMIS® measures of self-efficacy for managing chronic conditions. *Qual Life Res* 2017: 1-10.
95. Sullivan MJ, Bishop SR, Pivik J. The pain catastrophizing scale: development and validation. *Psychol Assess* 1995; **7**(4): 524.
96. Snaith R, Hamilton M, Morley S, Humayan A, Hargreaves D, Trigwell P. A scale for the assessment of hedonic tone the Snaith–Hamilton Pleasure Scale. *The British Journal of Psychiatry* 1995; **167**(1): 99-103.
97. Slepian PM, Ankawi B, Himawan LK, France CR. Development and initial validation of the pain resilience scale. *The Journal of Pain* 2016; **17**(4): 462-72.
98. Hanley AW, Nakamura Y, Garland EL. The Nondual Awareness Dimensional Assessment (NADA): New tools to assess nondual traits and states of consciousness occurring within and beyond the context of meditation. *Psychol Assess* 2018.
99. Hanley AW, Garland EL. Mapping the Affective Dimension of Embodiment with the Sensation Manikin: Validation Among Chronic Pain Patients and Modification by Mindfulness-Oriented Recovery Enhancement. *Psychosom Med* 2019.
100. Hanley AWBHNG, E.L. Metacognitive processes scale. In Preparation.
101. Garland ELH, A.W. Mindful reinterpretation of pain sensations scale. In Preparation.
102. Walach H, Buchheld N, Buttenmüller V, Kleinknecht N, Schmidt S. Measuring mindfulness—the Freiburg mindfulness inventory (FMI). *Pers Individ Dif* 2006; **40**(8): 1543-55.
103. Kotov R, Bellman S, Watson D. Short Suggestibility Scale. 2004.
104. Bastien CH, Vallières A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med* 2001; **2**(4): 297-307.
105. Hunt CAH, M.A.; Mohr, J.; Williams, A.L. Assessing perceived barriers to meditation practice: Revision of the determinants of meditation practice inventory (DMPI-R). Under Review.
106. Kelley A, Bakshi V, Haber S, Steininger T, Will M, Zhang M. Opioid modulation of taste hedonics within the ventral striatum. *Physiol Behav* 2002; **76**(3): 365-77.
107. Robinson TE, Kolb B. Morphine alters the structure of neurons in the nucleus accumbens and neocortex of rats. 1999.
108. Petrovic P, Kalso E, Petersson KM, Ingvar M. Placebo and opioid analgesia--imaging a shared neuronal network. *Science* 2002; **295**(5560): 1737-40.
109. Greenspan JD, Craft RM, LeResche L, et al. Studying sex and gender differences in pain and analgesia: a consensus report. *Pain* 2007; **132**: S26-S45.
110. Deane KD, O'donnell CI, Hueber W, et al. The number of elevated cytokines and chemokines in preclinical seropositive rheumatoid arthritis predicts time to diagnosis in an age-dependent manner. *Arthritis & Rheumatology* 2010; **62**(11): 3161-72.
111. Karlson EW, Daltroy LH, Lew RA, et al. The relationship of socioeconomic status, race, and modifiable risk factors to outcomes in patients with systemic lupus erythematosus. *Arthritis & Rheumatology* 1997; **40**(1): 47-56.
112. Andersson JL, Jenkinson M, Smith S. Non-linear registration, aka Spatial normalisation FMRIB technical report TR07JA2. *FMRIB Analysis Group of the University of Oxford* 2007; **2**.
113. Jenkinson M, Beckmann CF, Behrens TE, Woolrich MW, Smith SM. Fsl. *Neuroimage* 2012; **62**(2): 782-90.
114. Worsley K. Statistical analysis of activation images in Functional MRI: An Introduction to Methods. Jezzard, P., Matthews, PM, & Smith, SM, eds. OUP; 2001.
115. Seligman ME, Rashid T, Parks AC. Positive psychotherapy. *Am Psychol* 2006; **61**(8): 774.