University of Kansas Medical Center
RESEARCH PROTOCOL INVOLVING HUMAN SUBJECTS
TEMPLATE WITH GUIDANCE

Version date: 11-12-2019

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Study Title: Analgesic Effect of Music Listening During Pain Elicitation in Fibromyalgia

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I. Purpose, Background and Rationale
A. Aim and Hypotheses

I. ABSTRACT

Fibromyalgia can be thought of as a centralized pain state where pain is manifested and experienced in different body regions at different times. Individuals with centralized pain feel more pain than would be normally expected based on the level of nociceptive input. Music has previously been shown to have a positive effect on pain, anxiety, and depression in chronic pain patients. However, the impact of music listening on objective measures of pain sensitivity in patients with chronic pain have not yet been described. The goal of this pilot study is to begin to understand the possible analgesic effects of music listening on objective measures of pain sensitivity in patients with fibromyalgia. Previous studies in patients with FM have shown that patients have reduced self-reported pain, increased mobility, and activation of the descending pain modulatory system in the brain after even a short, 5 to10-minute music listening intervention. Our proposed study will be the first to investigate whether objectively measured pain sensitivity is reduced by music listening in these patients.

This two-arm parallel randomized controlled pilot study will enroll 40 patients with fibromyalgia. Patients' pain thresholds and sensitivity will be measured using a battery of quantitative sensory tests (QST). All patients will have two testing sessions: one under testing as usual conditions with no-sound, and one while listening to either instrumental Classical music, selected by the researchers with careful consideration of the musical characteristics, or a nature sound placebo control condition. This careful experimental design will allow us to test whether music listening elicits greater analgesic effects over simple auditory distraction. To minimize potential bias we will employ sound cancelling headphones and randomization of conditions so that the researcher collecting the QST measures will be blinded to whether the patient is hearing music, nature sounds, or nothing. The proposed study is significant as it will identify whether music listening has an analgesic effect during pain threshold and tolerance testing for patients with FM that supersedes any effect of auditory distraction. Results from the proposed study may provide objective evidence that music listening objectively improves analgesia and pain management and thus could be considered therapeutic during situations where acute pain is expected

II. SPECIFIC AIMS

Aim 1: Determine whether music listening during pain sensitivity testing has an analgesic effect on pain thresholds and tolerance and whether this effect is of greater magnitude in comparison to a non-musical auditory stimulus in patients with Fibromyalgia (FM). In order to accomplish this Aim, patients with FM will undergo a variety of quantitative sensory testing (QST) procedures in order to

fully characterize their peripheral and central nervous system pain processing systems, including mechanical pain sensitivity and temporal summation. QST testing will be done at baseline (no auditory stimulus of any kind) and then will be repeated within the same subject while listening to the auditory stimulus. Patients will be randomized to either the Music arm or the Placebo (nature sounds) arm. Half of the patients will listen to music, and half will listen to nature sounds during testing. Hypothesis 1a: We hypothesize that both listening conditions will reduce pain sensitivity (lead to higher pain thresholds and tolerance) as compared to the no-sound control. Hypothesis 1b: We hypothesize that the use of music listening during QST tasks will reduce pain sensitivity as compared to the use of only nature sounds.
Aim 2: Identify whether the objective analgesic effects of music listening are associated with subjective measures of anxiety, pain catastrophizing, resilience, and measures of music experience and enjoyment. In order to accomplish this Aim, the degree of analgesic effect of auditory listening (as measured by the difference in QST measures between baseline and music listening) will be calculated and correlated to subjective measures of pain and other pain-related patient characteristics using patient-reported outcome (PRO) measures. Hypothesis 2: We hypothesize that greater analgesic effect of music listening will be associated with lower levels of anxiety, depression, and with higher levels of music experience and enjoyment.

B. Background and Significance

Music has been shown to have an impact on the autonomic nervous system, reducing sympathetic nervous system activity leading to reduced heart rate and slowed respiration[1]. This in turn has been associated with reduction in anxiety[2]. Music listening also reduces acute pain during surgery[3], post-operative recovery[4], orthodontic procedures[5], and during the cold-pressor task (a pain induction technique) in healthy participants[6]. A recent meta-analysis confirms that music has a positive effect on pain, anxiety, and depression in chronic pain patients[7]. However, the impact of music listening on objective measures of pain sensitivity in patients with chronic pain have not yet been described. **The goal of this pilot study is to begin to understand the possible analgesic effects of music listening on objective measures of pain sensitivity in patients with fibromyalgia.**

Fibromyalgia (FM) is the second most common “rheumatologic” disorder, second only to osteoarthritis.[8] Depending on the diagnostic criteria used, the prevalence is from 2 to 8% of the general population.[9-14] With newer diagnostic criteria, the disease has a female:male ratio of 2:1, similar to other pain conditions.[14] The prevalence is similar in different countries, cultures and ethnic groups. There is no evidence that fibromyalgia has a higher prevalence in industrialized countries and cultures.[8,13] FM can be thought of as a centralized pain state. Centralized pain is a lifelong disorder that begins in adolescence or young adulthood where pain is manifested and experienced in different body regions at different times.[15-17] “Centralized” refers to the amplification of pain or central nervous system origins of pain. The term does not imply that peripheral nociceptive input is not a contributor to the individuals’ pain, but rather that they feel more pain than would be normally expected based on the level of nociceptive input. Not surprisingly, this “pain-prone” phenotype is best exemplified by fibromyalgia patients.[8]

Psychological, behavioral, and social issues also contribute to the pathogenesis of fibromyalgia. Individuals with fibromyalgia are more likely to have psychiatric disorders including: depression, anxiety, obsessive-compulsive disorder, and posttraumatic stress disorder (PTSD). Several factors appear to play a role in the pathophysiology of FM: abnormal autonomic nervous and neuroendocrine system function (disordered central pain processing), genetics (familial predisposition), and environmental triggers (psychosocial/life stressors and emotional/physical trauma).[18,19] Of these environmental triggers, traumatic experiences and stressful life events have been more frequently reported in FM patient cohorts compared to controls in clinical as well as population samples.[20,21]

There is a growing appreciation of the importance of augmented central nervous system (CNS) pain processing and centralized pain in many chronic pain states.[17,22] ***The term “centralized pain” has been used to describe any CNS dysfunction or pathology that may be contributing to the development or***

maintenance of chronic pain.[15,17,23] The pain experienced by individuals with centralized pain is typically multifocal (with a high current and lifetime history of pain in many bodily regions), rated as more severe, and characterized by neuropathic pain descriptors. Beyond pain, co-existing somatic symptoms including memory difficulties, fatigue, and sleep disturbances as well as cognitive/affective symptoms (e.g., catastrophizing, anxiety, depression) are frequently observed.[15,24,25] Another hallmark of the centralized pain phenotype is the frequent presence of hyperalgesia and/or reduced or absent endogenous analgesia.[26-28] Data from quantitative sensory testing (QST) studies suggest a wide, bell-shaped distribution in pain sensitivity across the general population. Most, but not all, individuals with centralized pain fall on the right side of this curve and have QST findings consistent with notable hypersensitivity (hyperalgesia and allodynia).[15,29-35] Some of the chronic pain conditions where QST evidence of widespread hypersensitivity is consistently seen include fibromyalgia (FM), irritable bowel syndrome, tension headache, low back pain, temporomandibular joint disorder, interstitial cystitis, and vulvodynia.[36-46] We will use QST to objectively measure pain sensitivity while listening to music and while listening to nature sounds, in patients with fibromyalgia.

The analgesic effect of music is thought to occur through several mechanisms: Contextual, Cognitive, Emotional, and Physiological[47]. First, music provides a predictable *context* that can increase the listeners' sense of control. This is further enhanced if the music is familiar, as this can bring in other effects that are not related to aspects of music specifically, such as setting up expectations and heightening nostalgia. Studies have shown the greatest analgesic effects when music is selected by participants. Second, music can serve as a *cognitive* distraction, taking attention away from the painful stimulus. This is of course not specific to music and could be achieved with other types of stimulation, such as reading or listening to nature sounds[48]. Third, music is a powerful inducer of *emotion*[49,50]. Music that is positive, liked by the listener, and low on arousal has the strongest analgesic effect[6]. Finally, music listening interventions and music therapy have also been shown to reduce anxiety and depression[51,52]. The anxiolytic effect may be due to the *physiological* effect of music on the parasympathetic nervous system, increasing the vagal response and reducing heart rate and respiration rate[2]. Music also has effects on the brain directly, causing the release of endogenous opioids and dopamine and activating areas of the descending pain modulatory system[53,54]. The specific musical characteristics that yield the greatest analgesic effects are difficult to pinpoint, as there is not a standard for reporting. Meta-analyses have revealed that music with 60-80 beats per minute, in a major key and without lyrics or percussion have the largest effects[55].

Previous studies in patients with FM have shown that patients have reduced self-reported pain and increased mobility after even a short, 10-minute music listening intervention. After listening to music of their choice, participants were faster in a standard mobility assessment, the timed-up-and-go task[56]. A second study using resting state functional magnetic resonance imaging (rsMRI) confirmed the impact of a 5-minute music listening intervention on the centralized descending pain modulatory system (DPMS), identified as changes in functional connectivity between regions of the DPMS that positively correlated with changes in pain scores[57]. Our proposed study will be the first to investigate whether objectively measured pain sensitivity is reduced by music listening.

The proposed study is **significant** as it will **identify whether music listening has an analgesic effect** during pain threshold and tolerance testing for patients with FM that supersedes any effect of auditory distraction. Results from the proposed study may provide objective evidence that **music listening objectively improves analgesia and pain management** and thus could be considered therapeutic during situations where acute pain is expected.

C. Rationale

The proposed study is significant as it will identify whether music listening has an analgesic effect during pain threshold and tolerance testing for patients with FM that supersedes any effect of auditory distraction. Results from the proposed study may provide objective evidence that music listening objectively improves analgesia and pain management and thus could be considered therapeutic during situations where acute pain is expected.

This study is innovative as it is the first to collect objective measures of within-subject change in pain

sensitivity in patients with FM using controlled, quantitative measures using a music listening intervention. Additionally, we will use specific pieces of classical music, clearly described in musical terms, for the listening intervention to control heterogeneity of response based on variability in musical parameters, such as tempo or instrumentation, which may impact the analgesic response. We will also use an active control condition of nature sounds to isolate the effect of music compared to another distracting stimulus. We have assembled a research team with expertise in chronic centralized pain syndromes and use of PROs and QST for clinical pain research (Nicol) and music (Lepping) to develop this research project, which will be utilizing rigorous methods currently used in Dr. Nicol's funded NIH work as well as having a strong foundation and rationale in music theory.

II. Research Plan and Design

Overall Study Design. For Aims 1 and 2, we will enroll 40 patients with FM to undergo QST testing on two separate days: baseline (Testing As Usual, no sound) and auditory listening. Participants will be randomized to two auditory listening conditions: music listening and nature sound listening. The conditions will be counterbalanced across subjects such that some will have listening on their first testing day and no sound on the second, and the rest of the subjects will have no sounds on the first day and listening on the second. Participants will be seated in a quiet room and a heart monitor will be attached. The participant will wear headphones during all testing sessions (including the no-sound control). They will listen to 10 minutes of the specified auditory recording (or silence) prior to QST testing. The researcher will then conduct the QST while the participant continues to listen to the auditory recording. The study visit will last for approximately 1 hour. The researcher collecting QST data will be blinded to which recording the participant is hearing.

After screening, informed eConsent (paper consent forms will be available if requested), and enrollment into the study, all subjects will undergo an evaluation which includes a battery of questionnaires for patient phenotyping that will assess symptoms including pain, physical function, depression, anxiety, and catastrophizing symptoms. QST parameters will also be performed after questionnaire administration as described above.

Patient Population. Recruitment: Participants will be recruited from the KUMC Marc A. Asher, MD, Comprehensive Spine and Pain Management Center's chronic pain clinics and surgical spine clinics. The Frontiers Registry and the Pioneers Community Research Recruitment Registry services through the Frontiers: The Heartland Institute for Clinical and Translational Research will also be used to foster the recruitment of participants from the community. We will also be using web-based recruitment pathways including Craig's List, social media, and the KUMC intranet. Patients will be paid for their time for all visits.

Randomization Procedures: Participants will be randomized following eConsent using the REDCap Randomization tool. Randomization is defined using a random number generator, and stratified by gender to ensure equal numbers of males and females in each group. Audio files will be labelled with dummy codes to blind the researcher collecting the data. A file will also be created for the no-sound condition, to further keep the researcher blinded.

Study Procedures / Outcome Measures.

Patient Characteristics Related to Pain and Music: This battery of questionnaires is intended to understand key aspects of pain, mood, and function as quickly and efficiently as possible.

- Demographics: Sex, age, race/ethnicity, marital status, education level, and body mass index (BMI) will be assessed in the context of standardized case report forms. Sex is an important biologic variable to investigate as centralized pain is more common in females, and is probably largely responsible for the fact that nearly any chronic pain condition is 1.5 – 2 times more common in women than in men.[58]

- Medication List: A list of the medications participants are taking for pain and medications that may impact heart rate or pain sensitivity (i.e. opioid or analgesic medications).
- Fibromyalgia-ness (FMness): FMness is a measure of pain and co-morbid symptom extensiveness and severity. It is calculated by combining the scores from the Widespread Pain Index with the Symptom Severity Scale from the 2011 FM Survey[59] to derive a continuous metric purportedly indicative of the degree of CNS pain amplification present in a given individual.[60]
- Fibromyalgia Functional Status: We will assess the current health and functional status in FM patients using the Revised Fibromyalgia Impact Questionnaire (FIQ-R).[61] The FIQ-R measures physical functioning, work status, and overall well-being.
- Clinical Pain Severity: Pain severity and functional interference due to pain will be assessed using the Brief Pain Inventory (BPI). The BPI is validated for chronic, non-malignant forms of pain, and asks patients to rate their current pain intensity, as well as their worst, least and average pain in the 7 days (0-10 NRS) and has been recommended by IMMPACT as a measure of choice for the assessment of pain in clinical research.[62-64]
- Depression and Anxiety: To avoid patient burden with the multiple domains, this study will take advantage of the static short forms developed by the NIH roadmap initiative PROMIS. The PROMIS short forms will be used for Depression and Anxiety.[65]
- Catastrophizing: Catastrophizing is associated with worse pain and the progression of chronic pain will be 6-item catastrophizing scale from the Coping Strategies Questionnaire(CSQ-CAT).[66]
- Music Experience: Participants will also rate their music listening habits (i.e. frequency, styles, reasons for listening, etc.) using the Brief Music Experience Questionnaire (MEQ)[67]. The Brief MEQ is a 53 item self-report measure of music centrality in the respondent's life, his or her musical aptitude, and experience with and reaction to music. Participants will also be asked to rate their familiarity with the music or sounds and how much they liked the music or sounds after each testing session.
- Impulsivity: Using the 27-item Kirby Delay Discounting Task, a type of impulsivity can be measured by determining the value participants see in rewards if they are offered at different time points (eg. $25 now OR $60 in 21 days). [81]

Quantitative Sensory Testing (QST): Pain testing will be performed using the Multimodal Automated Sensory Testing (MAST) System, a computerized QST device developed at the University of Michigan, and currently being employed in several clinical trials, including the NIH MAPP Network.

- Mechanical Pain Sensitivity (MPS). MPS will be assessed by applying discrete pressure stimuli to the thumbnail bed. The MAST system will deliver an ascending series of 5-s duration stimuli at 25-s intervals, beginning at 0.50 kg/cm2 and increasing in 0.50 kg/cm2 intervals up to tolerance or a maximum of 10 kg/cm2. Pain intensity will be rated after each stimulus on a 0 (no pain) – 100 (extreme pain) numerical rating scale (NRS). Pressure pain threshold and tolerance will be determined from this procedure, as well as the PAIN50, the pressure intensity that provokes a response halfway between threshold and tolerance.
- Temporal Summation (TS). TS is the perceived increase in pain intensity to repeated stimulation at a constant stimulus intensity and is believed to reflect central sensitization. A 256 mN pinprick stimulus (MRC Systems, Heidelberg, Germany) will be applied once to the forearm or hand, followed by a train of 10 identical stimuli (1 Hz). Following the single stimulus and the train of 10 stimuli, patients will report the pain intensity of the pinprick sensation using a 0-100 NRS. This procedure will be repeated 3x. The mean pain rating of the three stimulus trains will be divided by the mean pain rating of the single stimuli to calculate a wind-up ratio (*WUR*); a WUR >1 indicates temporal summation.[82]

Music and sound delivery: Auditory stimuli will be presented using an iPod and Bluetooth noise-cancelling headphones. Listening will begin 10 minutes prior to QST and will continue for the duration of the QST, for a total of 1 hour and 10 minutes. The listening condition will be a single bout on one of two days of testing. This is a two-arm parallel design RCT with Testing as usual (no-sound) and placebo control (nature sounds).

Heart Monitoring: Subject's electrocardiogram (ECG) will be recorded with a measurement device (Biopac/AcqKnowledge software) that consists of a computer-operated recording device and amplifier. The recording device and amplifier are attached to standard snap-on ECG electrodes. Three ECG electrodes are placed: one under the collar bone, one under the rib cage on the opposite side, and a ground on the abdomen. ECG will be recorded throughout each testing session. The time of each condition (passive listening vs. active listening with sensory/pain stimulus) will be recorded by the investigator. The ECG will be uploaded to Kubios software for analysis. Metrics of heart rate and variability in time-, frequency, and non-linear domains will be compared between conditions (passive vs. active listening) and between sounds (nature sounds vs. music).

Music characteristics: The musical selections will be professional recordings of instrumental Classical music selected by the researcher (See Appendix 1). All participants will hear the same pieces in the same order. Instrumentation ranges from piano solo to full orchestra, but they are without lyrics or heavy percussion. Pitch ranges across the pieces, but is standard across participants and not controlled by either the participant or the researcher. Tempo for all of the pieces is slow (~60 beats per minute). The pieces are in either major keys or minor keys, but all consist primarily of consonant harmonies and sustained melodic phrases. Participants will control the volume to their individual comfort level.

Placebo control: Professional recordings of nature sounds selected by the researcher without added music will be used as the active placebo control condition. All participants will hear the same recording. This active control condition will allow for non-musical analgesic effects, such as distraction, to be controlled in the experimental design. Participants will control the volume to their individual comfort level.

Mitigation of bias: We propose to use several strategies to mitigate potential bias in this study. Participants will be randomized to experimental or placebo group, group allocation will be concealed from personnel and they will be blinded throughout testing and analysis. Patients cannot be blinded as they will know whether they are hearing nothing, music, or nature sounds during testing. Our counterbalancing of testing days will help to ensure that attrition is not affecting one condition to a greater degree than another. Finally, our strategy to avoid potential publication bias is that by having both a no-sound control and a placebo nature sound control, we will be able to determine whether a) there is an analgesic effect of distraction in this population, and b) whether that effect is greater for music over another distracting auditory stimulus.

Study Limitations and Plans to Overcome Them: Recruitment: We do not anticipate that there will be any difficulty with participant recruitment. Given the clinically significant volume of fibromyalgia patients seen at the Marc A. Asher, MD, Comprehensive Spine Center, we are confident that subject enrollment will be achievable within the allotted timeframe. Also, we plan on using the innovative recruitment programs available at KUMC to assist investigators with participant recruitment including the Frontiers Registry and the Pioneers Community

Research Recruitment Registry. Our project budget includes a financial incentive for patient participation which will aid in recruitment and compliance with study procedures.

B. Study Type and Design:

This study is a pre-post interventional parallel randomized control trial pilot study. We will enroll 40 patients with FM to undergo QST testing on two separate days: baseline (Testing As Usual, no sound) and auditory listening. Participants will be randomized to two auditory listening conditions: music listening and nature sound listening. The conditions will be counterbalanced across subjects such that some will have listening on their first testing day and no sound on the second, and the rest of the subjects will have no sounds on the first day and listening on the second. Participants will be seated in a quiet room and a heart monitor will be attached. The participant will wear headphones during all testing sessions (including the no-sound control). They will listen to 10 minutes of the specified auditory recording (or silence) prior to QST testing. The researcher will then conduct the QST while the participant continues to listen to the auditory recording. The QST testing battery will last for approximately 1 hour. The researcher collecting QST data will be blinded to which recording the participant is hearing.

After screening, informed eConsent, and enrollment into the study, all subjects will undergo an evaluation which includes a battery of questionnaires for patient phenotyping that will assess symptoms including pain, physical function, depression, anxiety, and catastrophizing symptoms. QST parameters will also be performed after questionnaire administration as described above.

C. Sample size, statistical methods, and power calculation

Statistical Analysis: Data analysis will be performed by the KUMC Department of Biostatistics. The data analyst will also be blinded to whether data was during the nature sounds or music listening condition. Once all data have been collected and summary scores have been calculated, the database will be locked. Only then will the blind be broken for whether the QST scores were associated with music or nature sounds, and the final statistical test will be conducted.

Aim 1 Analyses: Pain thresholds and temporal summation scores will be treated as continuous measures and normality will be assessed prior to analysis. QST data will be analyzed using a paired t-test or appropriate nonparametric test to detect changes within-subject changes in QST measures between nature sounds or music listening.

Aim 2 Analyses: Magnitude of changes in QST measures between nature sounds and music listening will be calculated and correlated to the subjective measures of pain and music that are administered via patient-reported outcome questionnaires. All measures will be treated as continuous measures and normality will be assessed prior to analysis. These relationships will be analyzed using Pearson's correlation testing.

Sample size for Study Procedures in Aims 1 and 2: It is not possible to conduct adequate power analyses for the aims as this pilot study will be the first to measure QST changes with a music listening intervention in this patient population. Sample sizes for studies included in previous meta-analyses ranged from 25 to 175. We will use the data collected in this pilot study to estimate effect sizes for the next application for a larger trial.

D. Subject Criteria

Inclusion and Exclusion Criteria:

Inclusions

- Patients with fibromyalgia syndrome, ages 18 and older
- Ability to read and speak English to allow for written informed eConsent, phenotyping, and patient-reported outcomes measures

- Willingness to refrain from alcohol and nicotine on day of QST
- Willingness to refrain from physical activity or exercise that would cause muscle and/or joint soreness for 48 hours prior to testing (routine exercise or activity that does not lead to soreness is acceptable)
- We will attempt to recruit individuals with no chronic daily use of adjunctive pain medications, including tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and gabapentinoids as these drugs can influence QST findings, or have individuals be weaned off of these meds at least two weeks prior to being studied. If we do need to allow individuals into these cohorts while on such medications because of pragmatic issues, this information will be recorded and patients will be asked to remain on a stable dose for at least two weeks prior to QST assessments.

Exclusions

- Inability to provide written informed consent
- Peripheral neuropathy or loss of sensation in the upper extremities which would preclude QST testing
- Severe physical impairment (e.g., blindness, deafness, paraplegia)
- Co-morbid medical conditions that may significantly impair physical functional status (e.g., history of non-skin malignancy, or autoimmune disorder)
- Illicit drug or unreported opioid use (unreported opioid use would be considered opioid abuse and thereby excluded)
- Medical or psychiatric conditions that in the judgment of study personnel would preclude participation in this study (e.g., malignancy, psychosis, suicidal ideation)
- Pregnant or nursing (self-reported)
- Liver failure
- Self-reported liver cirrhosis
- Self-reported hepatitis
- Artificial fingernails or nail enhancements (artificial nails can influence pain sensitivity for QST)
- Severe Cardiovascular disease (examples: history of myocardial infarction, unstable angina, severe coronary artery disease, congestive heart failure, or severe valvular abnormalities) that are self-reported by patient or by medical record
- Average daily opioid dosing of >15 mg oral morphine equivalents preoperatively (e.g., > two 5 mg oxycodone tablets/day or > three 5 mg hydrocodone tablets/day). Conversions will be made based on well-accepted conversion tools we have used previously.[79,80] The rationale to include some patients taking low dose opioids is to enhance the generalizability of the findings (opioids are common in patients with many pain states), while not causing confounding by including patients on very high doses of opioids which may be a cause of opioid induced hyperalgesia which closely resembles central sensitization

E. Specific methods and techniques used throughout the study

Study Procedures / Outcome Measures.

Patient Characteristics Related to Pain and Music: This battery of questionnaires is intended to understand key aspects of pain, mood, and function as quickly and efficiently as possible.

- Demographics: Sex, age, race/ethnicity, marital status, education level, and body mass index (BMI) will be assessed in the context of standardized case report forms. Sex is an important biologic variable to

investigate as centralized pain is more common in females, and is probably largely responsible for the fact that nearly any chronic pain condition is 1.5 – 2 times more common in women than in men.[58]

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- Impulsivity: Using the Kirby Delay Discounting Task, a type of impulsivity can be measured by determining the value participants see in rewards if they are offered at different time points (eg. $25 now OR $60 in 21 days). [81]

Quantitative Sensory Testing (QST): Pain testing will be performed using the Multimodal Automated Sensory Testing (MAST) System, a computerized QST device developed at the University of Michigan, and currently being employed in several clinical trials, including the NIH MAPP Network.

- Mechanical Pain Sensitivity (MPS). MPS will be assessed by applying discrete pressure stimuli to the thumbnail bed. The MAST system will deliver an ascending series of 5-s duration stimuli at 25-s intervals, beginning at 0.50 kg/cm2 and increasing in 0.50 kg/cm2 intervals up to tolerance or a maximum of 10 kg/cm2. Pain intensity will be rated after each stimulus on a 0 (no pain) – 100 (extreme pain) numerical rating scale (NRS). Pressure pain threshold and tolerance will be determined from this procedure, as well as the PAIN50, the pressure intensity that provokes a response halfway between threshold and tolerance.
- Temporal Summation (TS). TS is the perceived increase in pain intensity to repeated stimulation at a constant stimulus intensity and is believed to reflect central sensitization. A 256 mN pinprick stimulus (MRC Systems, Heidelberg, Germany) will be applied once to the forearm or hand, followed by a train of 10 identical stimuli (1 Hz). Following the single stimulus and the train of 10 stimuli, patients will report the pain intensity of the pinprick sensation using a 0-100 NRS. This procedure will be repeated 3x. The mean pain rating of the three stimulus trains will be divided by the mean

pain rating of the single stimuli to calculate a wind-up ratio (*WUR*); a WUR >1 indicates temporal summation.[82]

Music and sound delivery: Auditory stimuli will be presented using an iPod and Bluetooth noise-cancelling headphones. Listening will begin 10 minutes prior to QST and will continue for the duration of the QST, for a total of 1 hour and 10 minutes. The listening condition will be a single bout on one of two days of testing. This is a two-arm parallel design RCT with Testing as usual (no-sound) and placebo control (nature sounds).

Heart Monitoring: Subject's electrocardiogram (ECG) will be recorded with a wearable measurement device (Firstbeat Bodyguard 2) that consists of a battery-operated recording device and a cable. The recording device and cable are attached to standard snap-on ECG electrodes. The device is placed under the collar bone and the cable with ECG electrode is placed under the rib cage on the opposite side. The Firstbeat device records the ECG as soon as it is attached. The time of each condition (passive listening vs. active listening with sensory/pain stimulus) will be recorded by the investigator. The ECG will be uploaded to Kubios software for analysis. Metrics of heart rate and variability in time-, frequency, and non-linear domains will be compared between conditions (passive vs. active listening) and between sounds (nature sounds vs. music).

Music characteristics: The musical selections will be professional recordings of instrumental Classical music selected by the researcher (See Appendix 1). All participants will hear the same pieces in the same order. Instrumentation ranges from piano solo to full orchestra, but they are without lyrics or heavy percussion. Pitch ranges across the pieces, but is standard across participants and not controlled by either the participant or the researcher. Tempo for all of the pieces is slow (~60 beats per minute). The pieces are in either major keys or minor keys, but all consist primarily of consonant harmonies and sustained melodic phrases. Participants will control the volume to their individual comfort level.

Placebo control: Professional recordings of nature sounds selected by the researcher without added music will be used as the active placebo control condition. All participants will hear the same recording. This active control condition will allow for non-musical analgesic effects, such as distraction, to be controlled in the experimental design. Participants will control the volume to their individual comfort level.

F. Risk/benefit assessment:

Risks to the Subjects

Human Subjects Involvement and Characteristics: Subjects are recruited from the greater metropolitan Kansas City area (population 1.8 million). Subjects who are 18 years of age and older will be recruited (Aim 1). We plan to enroll 40 subjects.

Sources of Materials: Research material obtained from participants consists of questionnaire and physiologic data. These data are used for research purposes only and specific individual results are not provided to subjects or their families. There is no billing of subjects, their families, or third-party payers for the research assessments or any study procedures.

Potential risks: Pregnant female subjects will be excluded from the study and therefore we do not anticipate any pregnancy-related issues. Protected health information is not divulged to any outside party or the subject's personal physician unless requested in writing by the subject after full disclosure of risks.

Psychological Risks: There is a possible risk of discomfort associated with being asked personal questions about the participant's health history. Patients may refuse to answer any question on the questionnaires or surveys that may be uncomfortable. There is the possibility that psychiatric disorders could be incidentally

detected using measures such as the PROMIS Depression or Anxiety tools. Further, while this measure does not specifically query suicidal ideation, during the course of research such thoughts could be conveyed to research staff. Should psychiatric disorders and/or suicidal ideation be detected we will contact the participant's primary physician to communicate potential problems, or refer as appropriate. In cases where suicidal ideation is severe and the participant is in imminent danger, study staff will escort them to the emergency room.

Risks Associated with QST: QST may cause minor but temporary physical discomfort. Study personnel will be trained by the investigators to be sensitive to participant discomfort and concerns. Participants will be instructed that they can stop any QST procedure anytime that the pain or unpleasantness of the task becomes unbearable. There have been no significant adverse events associated with any of these procedures in the experience of its use at the Chronic Pain and Fatigue Research Center at the University of Michigan. Specifically, MAST testing may cause some temporary physical discomfort on the thumbnail. The MAST System incorporates a series of redundant mechanical, electrical, and software safety features to prevent patient injury in the event of user error or device failure, including a safety pin that the subject can turn to immediately remove the pressure actuator from his or her thumb. The test is terminated at or before 10 kg/cm^2 of pressure which is a commonly used maximum pressure level in human sensory testing and does not result in physical injury. Participants will always have personal control over the stimulus and can stop it at any time or express instructions to stop the stimuli. They can also withdraw their thumb from the device. However, these instruments may cause minor physical discomfort in the areas of testing that is expected to resolve within minutes of test completion.

Adequacy of Protection Against Risk

Recruitment and Informed Consent: Participants will be recruited from the KUMC Marc A. Asher, MD, Comprehensive Spine and Pain Management Center's chronic pain clinic. The Frontiers Registry and the Pioneers Community Research Recruitment Registry services through the Frontiers: The Heartland Institute for Clinical and Translational Research will also be used to foster the recruitment of participants from the community. Subjects will be recruited through fliers and advertisements on social media websites. A signed eConsent form within RedCap will be obtained from the subject. The eConsent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be emailed (or printed, if preferred) to the subject. Rebecca Lepping, PhD, Andrea Nicol, MD or Miranda Mc Millan, MS will personally provide information about study procedures and obtain their consent via RedCap. The informed eConsent interview will be conducted by the study staff and will include a verbal and written explanation of the study, including the purpose, testing procedures, time commitment, inclusion/exclusion criteria, risks and benefits, alternative treatments, confidentiality, compensation, study personnel contacts, and required regulatory information. All individuals will be given the opportunity to ask questions. Once all questions and concerns are addressed to the participant's satisfaction, the participant will sign the consent form electronically. Following informed consent, the study participant will be assigned an anonymous study identification number. The informed consent document will be stored securely in RedCap.
Andrea Nicol, MD will assess and determine candidacy for informed consent and this will only be allowed from the patient and not a proxy as this study requires patient participation for many testing procedures, we will only recruit those individuals with the capacity to provide consent themselves.

Protection Against Risk: All research data are maintained confidentially by numerical code in password-protected databases. All paper copies are filed by number in accordance with professional standards of privileged information. Confidentiality is strictly safeguarded by HIPAA-compliant standards. Empathetic and professional staff mitigates risk of embarrassment related to subject performance on cognitive testing. Protected health information is not divulged to any outside party or the subject's personal physician unless requested in writing by the subject after full disclosure of risks related to divulging protected health information.

Potential Benefits of the Proposed Research to the Subjects and Others

As this study is ascertaining changes in pain thresholds with an intervention of music listening, no potential benefits are expected for patients participating in the study.

Women and Minority Inclusion in Clinical Research

Inclusion of women: Women are included in all studies described. We will try to expect approximately equal gender distribution in the enrolled participants, however, fibromyalgia is more prevalent in women which may make recruitment of equal gender distribution difficult to attain.

Inclusion of minorities: All minority groups are encouraged to participate in this and all our research projects. In 2003, the University of Kansas Medical Center's outpatient population was composed of 18% African-American, 10% Hispanic, 1% Asian, and 3% other. We expect this proportion of minorities will be reflected in our enrollment.

Exclusion of Children: The tests and interventions would be quite invasive and demanding for children. Therefore, children are not included in the present study.

G. Location where study will be performed:

All portions of the study will occur at KUMC. All visits will take place at the Hoglund Brain Imaging Center.

H. Collaboration (with another institution, if applicable): NA

I. Single IRB Review for a Multi-site study (if applicable): NA

J. Community-Based Participatory Research (if applicable): NA

K. Personnel who will conduct the study, including:

1. Indicate, by title, who will be present during study procedure(s): PI, Co-I, Study Coordinator
2. Primary responsibility for the following activities, for example:
    a. Determining eligibility: Co-I, Study Coordinator
    b. Obtaining informed consent: PI, Co-I, Study Coordinator
    c. Providing on-going information to the study sponsor and the IRB: PI, Co-I, Study Coordinator
    d. Maintaining participant's research records: PI, Co-I, Study Coordinator
    e. Completing physical examination: Co-I, Study Coordinator
    f. Taking vital signs, height, weight: N/A
    g. Drawing / collecting laboratory specimens: N/A
    h. Performing / conducting tests, procedures, interventions, questionnaires: PI, Co-I, Study Coordinator
    i. Completing study data forms: PI, Co-I, Study Coordinator
    j. Managing study database: PI, Co-I, Study Coordinator

L. Assessment of Subject Safety and Development of a Data and Safety Monitoring Plan

A Data and Safety Monitoring Plan has been developed which covers participant confidentiality, adverse event definition and monitoring, the data quality and safety review plan, and informed consent. This is uploaded as a separate document.

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III. Subject Participation

A. Recruitment

Participants will be recruited from the KUMC Marc A. Asher, MD, Comprehensive Spine and Pain Management Center's chronic pain clinic. The Frontiers Registry and the Pioneers Community Research Recruitment Registry services through the Frontiers: The Heartland Institute for Clinical and Translational Research will also be used to foster the recruitment of participants from the community. Subjects will be recruited through fliers and advertisements on social media websites, Craig's List, and the KUMC intranet. A signed eConsent form will be obtained from the subject. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be emailed (or printed, if preferred) to the subject. Rebecca Lepping PhD, Andrea Nicol, MD, or Miranda McMillan, MS will personally provide information about study procedures and obtain their written consent. The informed consent interview will be conducted by the study staff and will include a verbal and written explanation of the study, including the purpose, testing procedures, time commitment, inclusion/exclusion criteria, risks and benefits, alternative treatments, confidentiality, compensation, study personnel contacts, and required regulatory information. All individuals will be given the opportunity to ask questions. Once all questions and concerns are addressed to the participant's satisfaction, the participant will sign the consent form. Following informed consent, the study participant will be assigned an anonymous study identification number. The informed consent document will be stored securely in RedCap.
Andrea Nicol, MD will assess and determine candidacy for informed consent and this will only be allowed from the patient and not a proxy as this study requires patient participation for many testing procedures, we will only recruit those individuals with the capacity to provide consent themselves.

B. Screening Interview/questionnaire. Potential participants will be screened by telephone to determine whether they are a candidate for the study and are interested in participating. These will be patients who either contact us via recruitment flyers, emails, or social media or direct screening of patients through Dr. Nicol's chronic pain clinic. This information will be stored in RedCap. If the patient is eligible and comes in for testing, the researcher will go over their pre-screen information and note any changes.

C. Informed consent process and timing of obtaining of consent

The consent form will be emailed or mailed to the participant at the time that they are scheduled for the study visit to allow adequate time for review prior to the visit. The participant will be given a phone number to reach the PI, Co-I, and study coordinator if they have any questions prior to the visit. The study coordinator and/or PI or Co-I will go over the consent form in person the morning of the first study visit and answer any additional questions at that time.

D. Alternatives to Participation. N/A

E. Costs to Subjects. There is no cost to the subjects for participation in this study.

A. How new information will be conveyed to the study subject and how it will be documented. If any new information regarding study or research procedures during the course of the study period, the PI (Rebecca Lepping, PhD) will convey this information directly to the patient via telephone call and written letter mailed to the patient's listed home address.

B. **Payment, including a prorated plan for payment.**

Subjects will receive a total compensation of $100 for participation in this study. They will be given a ClinCard, which works like a debit card. After the Screening Phase is complete, payment will be added to the card by computer, after all study procedures have been performed. The money will be available within 1 business day. Subjects can use the ClinCard at an ATM or at a store. They will be given one card during the study. The KUMC Research Institute will be given their name, address, social security number, and title of this study to allow them to set you up in the ClinCard system. Study payments are taxable income. A form 1099 will be sent to the subject and the Internal Revenue Service if your payments are $600 or more in a calendar year. The subjects' personal information will be kept on a secure computer. It will be removed from the computer after the study is over and the money on the card has been used. The information will not be shared with other businesses. It will be kept confidential.

C. Payment for a research-related injury. We will include the following text in the consent form:

"All forms of medical findings, whether routine or experimental, involve some risk of injury. In spite of all safety measures, you might develop medical problems from participating in this study. You must report any suspected illness or injury to the study coordinator immediately. If such problems occur, you will be provided with emergency medical treatment and the investigator will assist you in getting proper follow-up medical treatment. Neither the investigator nor the sponsor will provide compensation for research-related injuries. Payment of lost wages, disability or discomfort is not available. You do not give up any of your rights by signing this form."

IV. Data Collection and Protection

A. Data Management and Security:

The PI, Co-Investigators, Research Coordinator, and Biostatistical faculty and staff will have access to de-identified study data. Only Dr. Lepping (PI), Dr. Nicol (Co-I) and study coordinator/research assistant Miranda Mc Millan, MS will have access to identified forms and data.

- Subject data will be coded (assigned a unique anonymous study number), which will allow the researchers to link the data to other information provided through questionnaires and study procedures. The code key linking the subject to their data will be maintained in a confidential file with standard security precautions. The key will only be used to connect study information to the data. The code will never leave KUMC. A breach of confidentiality will be considered a serious adverse event and will be reported to the KUMC IRB within 5 days of occurrence and a remediation plan will be put in place immediately. Records will be retained for 3 years per university and federal (NIH) policy.
- Paper copies of questionnaires will be maintained in the KUMC Hoglund Brain Imaging Center offices, in a locked room with access only to research team members. Patient information will only be stored on encrypted, fire-walled, databases which will limit access to patient identifying information to only those with assigned appropriate permissions such as: study team members, research assistants, and study coordinators. Research investigators will only have access to the de-identified information where the participant will be identified by their unique study ID number only. Only one data file will contain the linkage of subject identity and subject ID number. The Department of Biostatistics ensures data security by managing all data on a secure server that has role-based access that is password protected. All files that are modified are backed up daily, with complete backups of the server on a weekly basis. All data are stored in a HIPAA compliant manner. The code for linking individual subjects with their data is kept in a separate location from their research data files, under lock.

- This study will also use REDCap electronic data capture system. Survey distribution is through a personalized link specific to the patient. This link will be accessed during the testing session by the researcher and will not be shared with anyone outside the study team.

B. Sample / Specimen Collection

N/A

C. Tissue Banking Considerations: N/A

D. Procedures to protect subject confidentiality:

Several measures have been taken to reduce the risk of breach of confidentiality. These include training of study team members, electronic and physical security measures for data capture and storage, and collecting a minimum of identifiable information for each individual participant. The study team will take all possible steps to protect the privacy of subjects. This includes:

- Maintenance of protected health information (PHI) will include the assignment of a coded participant ID that will be used for accessing and merging of all records.
- Participant's data and specimens will be coded (assigned a unique study number) which will allow the researchers to link the data/specimens to other information that are provided through questionnaires and other study activities
- The code key linking the participant to their unique study number will be maintained in a confidential file with standard security precautions. The key will only be used to connect other study information to the data/specimens. This code will never leave the University of Kansas Medical Center.

A breach of confidentiality will be considered a serious adverse event. As such, it will be reported to the University of Kansas Medical Center IRB within 5 days of occurrence per University policies and procedures, and a remediation plan will be put in place immediately.

E. Quality Assurance / Monitoring

The study team will perform biannual source data verification and self-assessment of records to ensure that data are accurate.

V. Data Analysis and Reporting

A. Statistical and Data Analysis

Statistical analyses will be performed at the completion of each Aim.

B. Outcome

We expect to observe an analgesic benefit via improved pain thresholds in fibromyalgia patients undergoing QST when listening to music.

C. Study results to participants

No study results will be given to participants.

D. Publication plan

Publication of the results of this study will be governed by the policies and procedures developed by the study team.

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