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Cover Letter

Study Title: Brain Mechanisms Supporting Chronic Pain Relief by Meditation
NCT: NCT03354585
ICF Version and Approval Date: V28 14Feb2023
Local IRB Number: 181814
Sponsor: The National Institutes of Health
Institution: University of California San Diego Center for Pain Medicine

University of California, San Diego
Consent to Act as a Research Subject

Study Title:	Brain Mechanisms Supporting Chronic Pain Relief by Meditation
Protocol Number:	UCSD HRPP Project# 181814
Sponsor:	The National Institutes of Health
Institution:	UC San Diego Center for Pain Medicine
Investigator:	Fadel Zeidan, PhD
Address:	9452 Medical Center Drive La Jolla, CA 92037
Telephone Number:	(858) 405-3068

Before you decide whether to participate in this research study, it is important for you to understand why the research study is being done and what it will involve.

The decision to participate in this study is up to you. Your participation is completely voluntary. Your decision will not affect your relationship with your regular doctor or your current or future medical care.

Feel free to discuss this study with your family, friends, and healthcare provider before you make your decision whether to participate. Ask about anything you don't understand or would like explained better. Take time to decide whether or not you want to take part in this study.

Who is conducting the study, why you have been asked to participate, how you were selected, and what is the approximate number of participants in the study?
Dr. Fadel Zeidan is conducting a research study to find out more about ways to understand and help people with chronic pain. You have been asked to participate in this study because you are interested in learning mindfulness and have been diagnosed with chronic low-back pain. Your participation is voluntary. There will be approximately 120 participants enrolled at this site. We will randomly assigned 40 subjects to each group for the initiation of the final phase of the study.

Why is this study being done?
The purpose of this study is to see if mindfulness alters brain activation in response to raising your leg that may produce the feeling of pain. A technique called functional magnetic resonance imaging (fMRI) allows scientists to determine which parts of the brain are active during a particular task. This study will provide new information about how mindfulness affects the brain.

What will happen to you in this study and which procedures are standard of care and which are experimental?
If you agree to be in this study, the following will happen to you:

Study Session 1: You will first report to the UCSD Center for Functional MRI. After signing this consent form (if you choose to do so), you will complete our study questionnaires and will teach you to use our, what we call, visual analog scales to show us how you feel (about pain,

mood, etc.). This "11-point Likert scale" will also be administered at each MRI session assessing the neural mechanisms of mindfulness training. We will also administer heat stimuli to your leg that may produce the feeling of pain.

Chronic low-back pain inducing procedure: A trained research technician will perform the low back pain evoking procedure which is commonly used to assess the level of mobility and pain severity you may or may not have. This procedure can increase the feeling of pain for 10-15 minutes. In this study session and the follow up sessions, we will you test to see if this procedure increases your feeling of pain and whether or not you want to participate in our study.

A trained study technician will first instruct you to lie down on your back for 15 seconds and then we will ask you if you feel any pain.

We will then see if the angle and height needed for you to increase pain by 2 points on our scale and hold the position of your legs with 10 seconds or so. After lowering your legs, we will assess your pain ratings again. We will wait until your pain returns to normal before proceeding. After completing your questionnaires, you will be dismissed from this session and we will help you schedule the follow up sessions. We expect this session to take less than 1.5 hours to complete.

Heat Testing: An electrical device will deliver painful and non-painful thermal stimuli. The temperature of the stimulus can range from 35°C to 48°C. This temperature range has been used by a number of different laboratories including our own and will not cause any burns.

In all the MRI sessions, heat will be applied to the back of your calf and the back of your forearm. We will collect pain ratings, after each thermal pulse and/or after a series of stimuli, with the visual analog scale.

Thermal stimulation: As in all of our prior IRB approved experiments (Zeidan, Martucci et al. 2011, Lobanov, Zeidan et al. 2014, Zeidan, Emerson et al. 2015, Zeidan, Lobanov et al. 2015, Zeidan, Adler-Neal et al. 2016, Zeidan, Salomons et al. 2018, Adler-Neal, Emerson et al. 2019, Adler-Neal, Waugh et al. 2019), the MEDOC TSA-II will be used to deliver all thermal stimuli. All stimulus temperatures will be less than or equal to 48°C, and volunteers will be free to escape the stimulator at any time. No stimulus will produce tissue damage. This study will use a 16x16 mm surface area for the delivery of neutral and noxious stimuli. This modest stimulus area allows a relatively wide range of noxious stimuli to be delivered (up to 48°C for 30 seconds) without either tissue damage or significant subject withdrawals/drop-outs. Stimuli in this temperature range have been used extensively by the PI and numerous laboratories around the world and do not produce tissue damage or burns. In order to facilitate removal from the stimulator, the stimulator will be attached to a custom-designed thermal stimulation probe holder. Participants will place their calf on top of the probe holder and will not be strapped in or otherwise restrained. Therefore, participants will be able to simply lift their legs at any time.

Study Session 2: MRI 1: This session will be conducted at the UCSD Center for Functional MRI. You may have the option to attend the interventions via Zoom on an iPad after the first session.

- *Functional MRI Sessions*

The fMRI scans allow us to view the function of your brain. Four hours prior to the fMRI scan, you should not smoke, use other tobacco products, take any type of medications, and you should not drink coffee or other drinks with caffeine. During the MRI scan you will be in a cylindrical machine for up to two hours. We will fit you with a belt around your chest/belly to measure respiration rate and an oximeter on your index finger to measure heart rate. We will then place you inside the scanner. A special device will hold your head still during the scan. Each series of scans takes several minutes and there will be a rest period of a few minutes between scans. Before some of the scans, we will ask you to raise your leg that may or may not produce the feeling of pain with the assistance of a trained clinician and we will subsequently ask you to rate your feeling of pain. We will also place your leg on a custom made holder that is attached to the heat stimulating device. You will be able to lift your legs at any time. This device will deliver painful and non-painful thermal stimuli. The temperature of the stimulus can range from 35°C to 48°C. We will assess your pain ratings (if there are any) after each thermal heat stimulation series. We will scan your brain to determine the brain regions that are activated in response to this procedure. You will also receive scans looking at brain structure. It is very important for the study for you to be comfortable in the scanner. If you are not comfortable, please let us know at any time and we can take you out or try to make you more comfortable. The MRI technicians will be only a few feet away and you will be in constant communication via an intercom system.

We expect this (and every MRI session) session to take less than 1.5 hours to complete.

After completion of this session, you will be *randomized* to one of two groups, a mindfulness training intervention or a book-listening intervention.

You will be assigned by chance to a study group. Your chance of being assigned to each group is 1 in 2. Neither you nor the researcher(s) can choose the group to which you will be assigned.

Study Sessions 3-8: Regimen Sessions 1-6: The following sessions will be held at the UCSD Center for Mindfulness. Each of these sessions will take less than 45 minutes to complete. You may have the option to attend the interventions via Zoom on an iPad after the first session.

There will be no heat testing during these sessions.

Mindfulness Training:
Mindfulness training is based on a meditation technique called mindfulness, where we teach you how to relax and maintain a focused state of mind. **There is no religious or spiritual association with this practice.** Meditation training will be led by a teacher with extensive training and practice in mindfulness meditation. There will be up to a total of twelve meditation-training sessions. Each session will meet for approximately thirty minutes. In each session, you will be asked to close your eyes, relax and to be seated upright in a chair or lay flat on a mat.

Book-Listening Control Regimen: If you were randomized to this group, you will listen to an audio recording of *The Natural History and Antiquities of Selborne* in a quiet room across 12 sessions (20mins each session). You will not be allowed to sleep, use telephones, or talk to the experimenter during the control sessions.

Study Session 9: Post-Regimen MRI 2: After completing the first six sessions of mindfulness training or listening to a book, you will report to the MRI Center again. We perform the exact same procedures described in Study Session 2's MRI session. Yet, if you were randomly assigned to the mindfulness group, then you will be asked to practice mindfulness during and after the leg raise test.

How much time will each study procedure take, what is your total time commitment, and how long will the study last?

* The first study session will take about 1.5 hours.

* Each MRI session will generally take approximately one to 1.5 hours of your time.

* Each meditation session will take approximately forty-five minutes.

We will do our best to make the scheduling of the experiment meet your convenience. This study should not take more than 6 weeks to complete.

What risks are associated with this study?

Participation in this study may involve some added risks or discomforts. Possible risks and discomforts are detailed below; however, there may be other risks and side effects that are not yet known.

1) Straight Leg Raise Test

The straight leg raise test may produce the feeling of pain. Our goal is to produce a targeted 30% increase in the feeling of pain for no more than 20 minutes. Although rare, you may also feel discomfort and/or pain for up to 24 hours. We will do all that we can to ensure your comfort and/or safety during this procedure. Importantly, you will have complete control of how much you raise your leg.

2) MRI

The MRI scan is not associated with any known risks to your health, but you may be uncomfortable because you will be lying in a small space. If you cannot tolerate this, the scan will be stopped immediately. In the MRI scanner, we will provide you with a "squeezeball" that you can squeeze which will subsequently end the scan. During scanning, the MRI machine produces loud noises, so your ears will be protected by plugs or specialized headphones. Persons with any electronic objects or certain metal objects in their head or body such as cochlear implants, pacemakers or aneurysm clips may not participate. A checklist of excluded metal objects will be presented to you by the MRI technician or study staff prior to the MRI scan. There is no radiation associated with this type of scan.

3) Reproductive Risks

Due to unknown risks and potential harm to the unborn fetus, sexually active women of childbearing potential must use a reliable method of birth control while participating in this study. Reliable methods of birth control are: abstinence (not having sex), oral contraceptives,

intrauterine device (IUD), birth control injection, tubal ligation, or vasectomy of the partner (with confirmed negative sperm counts) in a monogamous relationship (same partner). An acceptable, although less reliable, method involves the careful use of condoms and spermicidal foam or gel and/or a cervical cap or sponge. We encourage you to discuss this issue further with your physicians if you have any questions.

Pregnant women are excluded from participation in this study. Because some methods of birth control are not 100% reliable, a urine pregnancy test is required at least 10 days from your last normal menstrual period, if you are a sexually active woman of childbearing potential and not using reliable birth control.

4) Randomization

You will be assigned to a study group at random (by chance). Your assignment is based on chance rather than a medical decision made by the researchers. The study group you are assigned to might not be the group you would prefer to be in. Your assigned study group might also prove to be less effective or have more side effects than the other study groups(s), or other treatments available for your condition.

5) Thermal Stimuli

The purpose of this study is to study pain sensations, so you may feel pain produced by heating the skin to temperatures from 35°C (95°F; normal skin temperature) to 48°C (120.2°F). This temperature range has been used many times by Dr. Zeidan, the primary investigator (PI) of this study, and in many other studies around the world. Your body will not be damaged or burned in this study since the heat probe and the temperatures have been carefully chosen to produce the necessary sensations safely. This method has been used for many years with no harmful physical or psychological (mental) effects. However, in extremely rare cases, the computer controlled stimulator has been reported to malfunction and to cause a burn to the small skin region being tested. You will always be awake during the study and free to tell us to turn off the heat probe at any time. In addition, you will be able to remove the stimulated body part from the thermal probe at any time without any difficulty

Unknown Risks

There may be side effects that are not yet known. You should call your study doctor if you think you are having any of the problems listed above or even if you are having problems that are not on this list. Because this is a research study, there may be some unknown risks that are currently unforeseeable. You will be informed of any significant new findings.

Incidental Findings: When MRI scans are viewed for research purposes, incidental findings (such as a brain tumor, cyst, or lesion) may be observed. In some cases, incidental findings in the brain from the MRI scan may reveal a previously unknown health concern. However, as the scans performed are for research and not diagnostic purposes, incidental findings may not reflect a real problem if a diagnostic scan is performed later.

If we identify an incidental finding, we will have a neuroradiologist determine if a supplementary clinical MRI is needed.

If we find an incidental finding in your brain, would you like neuroradiologist to make an evaluation for further steps?

YES ☐

NO ☐

If we find an incidental finding in your brain, would you like us to inform you?

YES ☐

NO ☐

What are the alternatives to participating in this study?
You do not have to participate in this study. As this is not a treatment study, the only alternative to participating in this study is to not participate.

What benefits can be reasonably expected?
There may or may not be any direct benefit to you from these procedures. The investigator(s), however, may learn more about ways to benefit chronic pain patients in the future.

Can you choose to not participate or withdraw from the study without penalty or loss of benefits?
Participation in research is entirely voluntary. You may refuse to participate or withdraw at any time without penalty or loss of benefits to which you are entitled. If you decide that you no longer wish to continue in this study, you will be requested to talk to the investigators or study staff first. You will be told if any important new information is found during the course of this study that may affect your wanting to continue.

You will be told if any important new information is found during the course of this study that may affect your wanting to continue.

Can you be withdrawn from the study without your consent?
You may be withdrawn from the study for the following reasons:

1. Dr. Zeidan believed it was in your best medical interest not to participate.
2. You had an unexpected reaction.
3. You failed to follow instructions given to you by the study personnel.
4. The entire study was cancelled.
5. If you there are accruing absences and/or tardiness to study sessions.

Will you be compensated for participating in this study?
In compensation for your time and travel, you will receive up to $780.00 for participating in this research.

You will be paid $30.00 for each experimental session (total of 9 sessions = $270.00) that you successfully complete and a supplemental $30.00 for each pain testing session (total of 3 pain

testing session = $90.00) in the laboratory. In the MRI portion of the study, you will receive an additional $50.00 for undergoing an MRI scan of brain activation (total MRI payments = $100.00). You will also receive an additional $ 40 for successfully completing all study sessions The total payment for completing the entire study is $500.

Are there any costs associated with participating in this study?
There will be no cost to you for participating in this study.

What if you are injured as a direct result of being in this study?
If you are injured as a direct result of participation in this research, the University of California will provide any medical care you need to treat those injuries. The University will not provide any other form of compensation to you if you are injured. You may call the Human Research Protections Program Office at 858-246-HRPP (858-246-4777) for more information about this, to inquire about your rights as a research subject or to report research-related problems.

What about your confidentiality?
Research records will be kept confidential to the extent allowed by law. The results of this research study may be presented at scientific or medical meetings or published in scientific journals. Your identity and/or your personal health information will not be disclosed unless it is authorized by you, required by law, or necessary to protect the safety of yourself or others. There is always some risk that even de-identified information might be re-identified.

Participant information may be provided to Federal and other regulatory agencies as required. The Food and Drug Administration (FDA), UCSD Institutional Review Board, and NIH, for example, may inspect research records and learn your identity if this study falls within its jurisdiction.

If you choose to participate in this study, your medical record at the University of California, San Diego will indicate that you are enrolled in a research study. Information about the research and any medications or devices you are being given as a participant may also be included in your medical record. This part of the medical record will only be available to people who have authorized access to your medical record. If you are not a patient at UCSD, a medical record will be created for you anyway to ensure that this important information is available to doctors in case of an emergency.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Who can you call if you have questions?
Dr. Fadel Zeidan and/or_____has explained this study to you and answered your questions. If you have other questions or research-related problems, you may reach Dr. Fadel Zeidan at (858) 405-3068.

You may call the Human Research Protections Program Office at 858-246-HRPP (858-246-4777) to inquire about your rights as a research subject or to report research-related problems.

Your Signature and Consent

You agree that you have been given a chance to ask questions about this research study. These questions have been answered to your satisfaction. You agree to participate in this study. You do not give up any of your legal rights by signing this informed consent form.

You will be given a copy of this signed informed consent form for your own records.

You agree to participate.

Subject's signature Date

_____ _____

Signature of person who explained consent: Date:

_____. _____

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