# Exercise and Neuromodulation in Women with Fibromyalgia: Neurophysiological Adaptations and Clinical Effects

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Sponsor: Universidad Andrés Bello

Principal Investigator: Edith Elgueta Cancino

## INFORMATION AND INFORMED CONSENT DOCUMENT

**Study Name:** "Exercise and Neuromodulation in women with Fibromyalgia: Neurophysiological Adaptations and Clinical Effects"

**Supervisor:**
**Principal Investigator:**

**Academic Unit:**

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The purpose of this information is to help you make the decision to participate in this research project, and to authorize the use of the information from your evaluations. **Read** this document carefully, you can ask the researcher as many questions as you need and take the time to decide.

### 1. INTRODUCTION AND OBJECTIVES OF THE RESEARCH

Central sensitization is the main mechanism that explains chronic pain in fibromyalgia. This is defined as an alteration in sensitivity and pain processing, that is, the presence and/or exaggeration of the perception of pain without evidence of any damage to body tissue that activates peripheral pain receptors. This central sensitization is characterized by a state of increased excitability or **hyperexcitability** of the neurons that process pain, that is, they have increased nerve conduction that causes an exaggerated response or hyper-reaction to be generated at the slightest stimulus. This hyperexcitability can affect the nerve pathway that connects the brain and muscles (also called the corticospinal tract), leading to changes in how muscle contractions are controlled and consequently in activities of daily living and possibly in tolerance to exertion (fatigue). In other types of pain syndromes, hyperexcitability is known to be related to increased pain. However, in the case of fibromyalgia, **it is not yet clear whether all people are hyperexcitable, and whether this factor influences variations in pain contributing to the generation of chronic pain**. Similarly, it is still unclear whether this increased excitability directly affects feelings of fatigue, sleep, quality of life, psychosocial aspects, level of physical activity, aerobic capacity, endurance and muscle strength. Identifying this would be of great help in establishing specific treatment protocols to the causes of pain variations, thus making them more effective.

Among the existing treatment alternatives (drugs, exercise, neuromodulation, etc.), exercise has shown positive results for people with fibromyalgia. For example, those protocols that include **high-intensity aerobic exercise (HIIT)** have been shown to be effective in managing pain, fatigue, sleep, anxiety, depression, functional capacity, and improving quality of life in people with fibromyalgia. Similarly, the analgesic effect of neuromodulation tools such as **transcranial direct current stimulation (tDCS) is well known.** However, the

The effect of this type of intervention varies between individuals. These variations could be related to **corticospinal excitability (hypo or hyperexcitability),** but this has not been investigated in people with fibromyalgia. It has been hypothesized that the combination of HIIT and tDCS might be able to effectively modulate the excitability and cardinal symptoms (pain, fatigue, and sleep disturbances) of fibromyalgia.
That is why this project seeks to answer:

**Study 1**
Is corticospinal excitability increased (hyperexcitability) in women with fibromyalgia compared to women without fibromyalgia, and is it related to pain, fatigue, sleep, quality of life, psychosocial aspects, aerobic capacity, physical activity level, endurance and muscle strength?

The objective is to compare and associate corticospinal excitability with pain, fatigue, sleep, quality of life, psychosocial aspects, aerobic capacity, level of physical activity, endurance and muscle strength among women with and without fibromyalgia.

**Study 2**
Is the combination of high-intensity aerobic exercise (HIIT) and neuromodulation (tDCS) more effective than HIIT alone in changing corticospinal excitability, pain, fatigue, sleep, psychosocial aspects, quality of life, training adherence, enjoyment, aerobic capacity, endurance and muscle strength in women with fibromyalgia?

The aim is to compare the effects of high-intensity aerobic exercise, with and without active neuromodulation on corticospinal excitability, pain, fatigue, sleep, psychosocial aspects, quality of life, adherence, enjoyment, aerobic capacity, endurance and muscle strength in women with fibromyalgia.

To be invited to participate in this study you must meet the following criteria:

- Be between 18 and 65 years old
- Diagnosis by rheumatologist/physiatrist (according to 2016 American College of Rheumatology criteria)
- Stable medical treatment of symptoms at least 4 weeks prior to participation
- Moderate or severe pain (equal to or greater than 40 mm on the numerical scale) for more than 3 months
- Body mass index (BMI) between 18.5 and 39.9 kg m2
- Stable dose of medication for ≥4 weeks
- ≥40-point score on the central awareness inventory
- Controlled high blood pressure

**You will not be able to participate in the study if you have:**
Pain not related to fibromyalgia, of origin: carcinogenic, infectious, traumatic, localized neuropathic, isolated degenerative or inflammatory joint, severe headache. If you have undergone brain surgery, suffered **seizures/epilepsy**, cardiovascular, pulmonary, metabolic (type II diabetes) diseases, a history of stroke, and traumatic brain injury,

severe psychiatric disorders, severe depression (greater than 29 points on the Beck II depression inventory), consuming imipramine-bupropion-clozapine-benzodiazepines, having cochlear pacemakers, ferromagnetic and cardiac pacemakers, drug and alcohol abuse. Be currently pregnant and/or breastfeeding, under physiotherapy treatment, participating in a designed program of sports training or high-intensity aerobic exercise in the last 3 months prior to it on a systematic basis or have **a high cardiovascular risk to exercise according to** the PAR-Q questionnaire (**only for study 2**). Not speaking or reading Spanish fluently, inability to understand the pain scale and cooperate in testing.

## 2 INVESTIGATION PROCEDURES:

**What should I do if I decide to participate in this research project?**

Once you have agreed to participate in this study and have signed the informed consent, you will be invited to come to the Laboratory of Rehabilitation and Exercise Sciences of the Universidad Andrés Bello Campus Casona (Las Condes) for **an evaluation session** (3 hrs approx.) if you decide to only participate in **study 1**, you will be required to complete a series of questionnaires and evaluations (described below). If you decide to participate in **Study 2,** you will need to attend multiple times. First, 6 **exercise familiarization sessions** for two weeks (30 mins, each), so that you get to know and get used to the exercise modality progressively. Then, 1 **evaluation session** (pre-workout) followed by **12 training sessions** (3 sessions x 4 weeks) of high-intensity aerobic exercise on an exercise bike (30 min each session); to finish with **1** post-workout evaluation session. The first session will last approximately 3 hours, which includes physical evaluations and completion of the required questionnaires.

### 2.1 Study 1 - Evaluations

Questionnaires: To begin with, the researcher will explain all the procedures, then we will ask you to complete a series of questionnaires that seek to better understand fibromyalgia and its symptoms. The questionnaires will have questions focused on describing quality of life, sleep, fatigue, pain sensation, and psychosocial characteristics. Specifically, how you respond to an experience of pain, how you accept pain, whether you have fear of movement, depression, and/or anxiety. We will ask you questions about your willingness to commit to a physical exercise program, how much exercise you regularly do (physical activity level), whether you enjoy physical activity, and other questions related to your habits that will allow us to determine if you are eligible for exercise (cardiovascular risk for exercise), if you participate in Study 2.

Pressure pain thresholds: We will evaluate the first indication of pressure pain or "pain threshold" for this using a tool that has a 1 cm diameter rubber head called an algometer, we will press on the skin at 4 specific points of the body (supraspinatus, buttocks, knee and lateral epicondyle of the elbow on both sides of the body). The pressure will gradually increase until you first identify the first sign of pain. This procedure will be repeated 3 times per stitch ***(see image 1).***

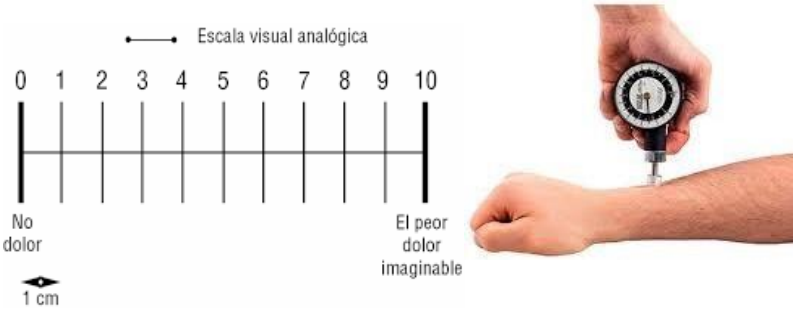


Image 1. Pain assessments on scales of 0/10 – 0/100 and a 4-point pain monitor on the body as shown in the images.

Excitability: Using a small magnetic field we will assess how your brain communicates with your muscles using a technique called transcranial magnetic stimulation ***(see image 2).*** This stimulation will be delivered over your head using a coil the size of a pingpong paddle. **This procedure is non-invasive, safe and painless where it has been widely used to evaluate and treat different pain and other conditions**. During the evaluation you will hear a **"click"** sound with each stimulation, this sound can be annoying so you will use earplugs that will be provided to decrease the volume of the noise. The sensation that this type of evaluation produces has been described as the sensation of receiving a gentle blow on a bicycle helmet and is painless.

Image 2. Evaluation of corticospinal excitability through transcranial magnetic stimulation as shown by the images.

Muscle activity: We will also ask you to do a small activation of your leg muscles during stimulation while observing your level of contraction on a screen. We will place a pair of electromyography electrodes that will be glued to the skin with a hypoallergenic adhesive tape. These electrodes will allow us to record the responses of your muscles ***(see image 3).***

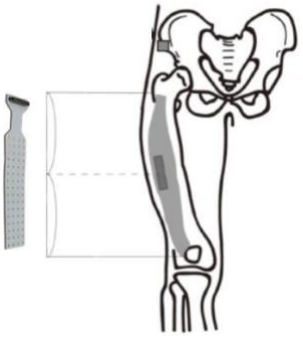

Image 3. Position of electromyography electrodes to record muscle response as shown in images.

Muscle strength: After this evaluation, the maximum strength and muscular endurance of your legs will be measured. You will first be asked to contract your leg towards knee extension with maximum force for 5 seconds (it will be repeated 3 times) with a 2-minute rest between each one. You will then be asked to perform a submaximal muscle endurance test, this means that you will be asked to keep the muscle in contraction for as long as possible (until you can't take it anymore) at about 20% of your maximum strength ***(see image 4).***

Image 4. Evaluation of thigh muscle resistance and strength as shown in the image.

Aerobic Capacity: And finally, your aerobic capacity on a bicycle and a mask over the nose-mouth that measures gases such as the oxygen you use in the test will be evaluated. This test is incremental, i.e., minute by minute the intensity of the exercise will increase until the primary criterion (change of less than 150ml between successive loads) or 2 of the secondary criteria (blood lactate ≥8 mM, RER ≥1.15, increase of 10 beats per minute in the estimated maximum heart rate, and Borg or perception of exertion ≥17) ***(see image 5)***. In addition, during the measurement, heart rate (with a watch and sensor that is placed on the chest), oxygen saturation and dyspnea (feeling of shortness of breath during exercise) will be evaluated.

Image 5. Evaluation of aerobic cycling capacity as shown in the image.

Height and body composition: In addition, height will be evaluated by standing without shoes on the stadimeter where a stop is placed on your head to measure your height. And body composition is evaluated standing on the InBody without shoes or socks, taking two handles with your hands, opening your arms, holding the position for a few seconds, and you should attend on an empty stomach for 3-4 hours ***(see image 6).***

Image 6. Assessment of body composition through the InBody.

**2.2 Study 2**

Study 2 consists of a stage of familiarization to the exercise, pre-intervention evaluation, intervention and post-intervention evaluation. Once you have signed the informed consent, you will begin the familiarization stage.

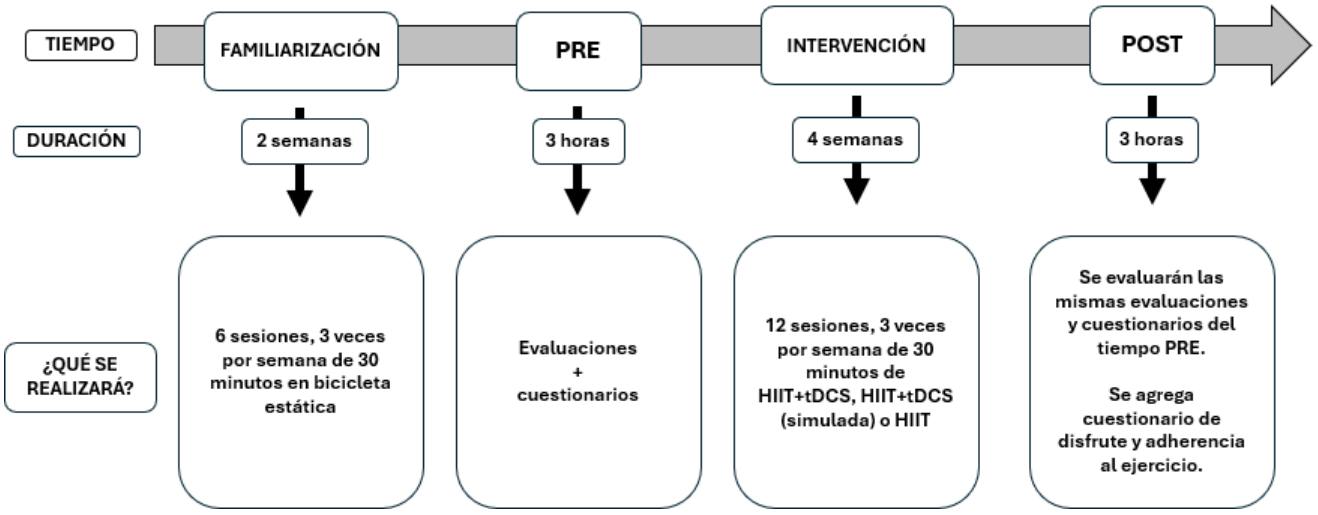


Figure 2. Illustration of the evaluation protocol of study 2 in time, duration and what will be carried out.

**2.2.1 Familiarization exercise:** for 2 weeks, you will perform a familiarization protocol of 3 times a week (6 sessions, 30 minutes) of HIIT cycling at a moderate to high intensity (between 80%-95% of maximum heart rate), which will gradually progress from 2 intervals of 15 seconds in duration, to 5-7 intervals of 45 seconds in duration.

**2.2.2 Pre- and post-intervention evaluations:** after 2 weeks of familiarization and at the end of the 4-week intervention program, the same evaluations described above will be carried out (study 1).

**2.2.3 Intervention Protocols:** After the pre-intervention assessment you will be randomly assigned to one of three groups of high-intensity aerobic exercise **(HIIT).** HIIT training will last for 4 weeks, 3 times a week (12 sessions):

**Group 1 - Exercise (HIIT) + neuromodulation (tDCS):** During HIIT exercise, neuromodulation will be applied for which 2 electrodes will be placed on your head, these will generate a tingling sensation that can last 20 minutes ***(see image 7).***

**Group 2 - Exercise (HIIT) + neuromodulation (simulated tDCS):** During HIIT exercise, simulated neuromodulation will be performed for which 2 electrodes will be placed on your head, which will generate a tingling sensation with ramps 30 seconds at the beginning and end of the training session.

**Group 3 – Exercise (HIIT):** You will perform the HIIT protocol alone at an intensity between 80%-95% of your maximum heart rate.

- **High-intensity aerobic exercise (HIIT):** During this protocol you will be seated on an exercise bike which will be adjusted to your height and resistance. You will perform a protocol consisting of 1 minute of cycling with high-intensity resistance with a "hard to pedal" workload, to achieve an effort equivalent to 80%-95% of maximum heart rate, followed by 2 minutes of recovery, this protocol will be repeated 10 times (1x2x10, 30 minutes total). Recovery consists of a 2-minute period of rest in which you stay on the bike (without pedaling) until recovery is achieved, evidenced by a drop in heart rate below 70% of the maximum. If you do not recover within 2 minutes, you will be allowed a longer rest time until you reach your expected heart rate.
- **Neuromodulation - transcranial direct current stimulation (tDCS):** this involves the use of a low-intensity electrical current that is capable of stimulating the cells of your brain, this type of stimulation is safe and painless. To do this, 2 neuromodulation electrodes will be placed on your head that will generate a tingling sensation that can last up to 20 minutes.
- **Neuromodulation - simulated transcranial direct current stimulation (tDCS):** this involves the use of a low-intensity electrical current that **will simulate** the sensation, but **will not stimulate** your brain cells only generating a tingling sensation that can last up to 20 minutes, this type of stimulation is safe and painless. To do this, 2 neuromodulation electrodes will be placed on your head.

Image 7. Transcranial direct current stimulation equipment and electrode position to be used during the exercise session.

- **Evaluations during the intervention:** Before, during and after each exercise session, the perception of pain, exertion, shortness of breath, heart rate, blood oxygenation and blood pressure will be evaluated.
  - **Stand and sit test 3 times: At the** beginning and end of each exercise session you will be asked to stand and sit in a chair three times assessing leg pain on a scale of zero to one hundred millimeters (0-100mm).
  - **Pain:** Your pain perception will be assessed on a numerical scale from zero to ten (0-10, 0= no pain, and 10= maximum pain) before and after the exercise session, as well as before and at the end of each 1-minute HIIT cycle.
  - **Effort:** Your perception of effort will be assessed on a numerical scale from 6 to 20 (6 = no effort and 20 = maximum effort) during exercise.
  - **Feeling short of breath:** will be assessed on a numerical scale from zero to ten (0-10, 0=no shortness of breath at all, and 10=severe shortness of breath or inability to continue exercise).
  - **Heart rate:** it will be measured with a sensor located on the chest and watch.
  - **Blood oxygenation:** This will be measured with a sensor located on the index finger (pulse oximeter).
  - **Blood pressure:** This will be measured with a pressure cuff (sphygmomanometer) in your arm.
  - **Diet:** You will have to complete a questionnaire with the diet consumed regarding the previous day and the day of the exercise session. In addition, you will be given instructions regarding the consumption of certain foods and preparation for evaluations.

## 3 PROCEEDS

Their participation will allow us to advance in the knowledge about the neurophysiological characteristics of people with fibromyalgia and the effects that high-intensity aerobic exercise has on pain, fatigue, sleep, psychosocial aspects, quality of life, aerobic capacity, endurance and muscle strength. **This knowledge will contribute to the advancement in creating more personalized training programs for people with fibromyalgia. This study will have direct benefits for you**, **as physical exercise has been shown to generate positive effects on pain, fatigue, sleep, quality of life, anxiety, depression, strength and aerobic capacity.** It is also known that the technique of transcranial direct current stimulation **can have analgesic effects** that could enhance the effects of exercise. Additionally, we will provide you with a free detailed report of your body composition detailing the distribution of fat and muscle throughout the body, made with a first-line instrument to evaluate body composition that is usually used in health centers and gyms at a high cost (InBody 770). We will also describe your aerobic capacity and muscle strength.

## 4 RISKS

It should be noted that all these evaluations and interventions used in this research project are non-invasive and painless. Although our strict selection criteria allow us to ensure the safety and minimum risk of the procedures for the volunteers, in all cases

There are some associated risks that can be classified as more likely and less likely:

- The **most likely** risks you may have are: Headache or local pain at the site of transcranial magnetic stimulation with a chance of **less than 2%,** and which is relieved by pain medication. Pain/burning sensation or irritation of the skin in preparation for positioning the electromyography electrodes.
- The **least likely** risks are: through transcranial magnetic stimulation it could induce a seizure, but the percentage of it occurring is minimal **less than 0.003%** because the most common causes for this are the pre-existence of epilepsy or neurological alterations. Transcranial direct current stimulation may cause burning, itching, or burning of the scalp. To minimize this risk, the pads that protect the scalp will be checked frequently and moistened. During exercise, you may have dizziness, nausea, fainting, chest pain, and vomiting. If this occurs, the training will first be stopped by placing it in a safe place and your recovery. If symptoms continue or worsen, the campus nurse will be called and will evaluate and provide first aid if needed. The situation will be evaluated and, if necessary, the institutional security protocol system will be activated.
- During the evaluations, 2 health professionals with postgraduate studies will be with you [redacted], in which they will monitor the situation and call the campus nurse.

## 5 COSTS

Your participation in this study will NOT have any associated costs or monetary rewards to you.

## 6 COMPENSATION

In case of any discomfort or side effect to exercise or to the evaluations described, an evaluation will be carried out by the laboratory team, and if required, free kinesic rehabilitation will be provided.

## 7 CONFIDENTIALITY OF INFORMATION

The information obtained will be kept confidential. The data obtained will be kept in a computer system as a backup, in addition to being written in a paper file that will be kept in a locked drawer which PhD [redacted] and [redacted] will have access only. In accordance with compliance with Law 20,584 on the rights and duties of people in health care, Personal Data Protection Law 19,628 and Law No. 20,120 on scientific research on the human being, the genome, and prohibition of human cloning. In addition, this research adheres to the Declaration of Helsinki based on ethical principles for medical research on human subjects. The information will be used only for the purpose of contributing to scientific knowledge and for the benefit of society. The results of this study may be presented at conferences/seminars and published as an article in a journal or online, whose name will not be known. The published results will not contain information that may be

used to identify volunteers unless specific consent has been obtained for this. You can ask the researcher for a copy of the published results if you wish.

## 8 VOLUNTARISM

Your participation in this study is **absolutely voluntary**. You have the right not to agree to participate or to withdraw your consent and withdraw from this research at any time you deem appropriate without having to give a reason, if you wish. By doing so, you do not lose any rights that assist you as a patient or student of this institution and the quality of medical or academic care you deserve will not be affected.

In the event that you do not wish to continue participating in this research, you must first inform the principal investigator **at** [redacted] through his email [redacted] and/or [redacted] and/or if you wish to contact the Bioethics Committee of the Faculty of Medicine of the Universidad Andrés Bello through the institutional email [redacted]

If you withdraw your consent, all data obtained up to that point will be used. We will do this by ensuring your confidentiality.

## 9 QUESTIONS

If you have questions about this medical research you can contact or call the Investigator Responsible for the study: Name: [redacted] This study was approved by the Scientific Ethics Committee of the Faculty of Medicine of the Andrés Bello University. If you have questions about your rights as a volunteer in medical research, you can write to the email: [redacted] the Scientific Ethics Committee, so that the president, [redacted] can refer you to the most appropriate person.

## 10 DECLARATION OF CONSENT STUDY 1 (RESEARCHER'S COPY)

- I have been explained the purpose of this research, the procedures, the risks, the benefits and the rights that assist me and that I can withdraw from it at any time I wish.
- I sign this document voluntarily, without being forced to do so.
- I am not renouncing any right that assists me.
- I will be informed of any new information related to the study that arises during the research and that may be of direct importance to me.
- I have been informed that I have the right to re-evaluate my participation in this research at my discretion and at any time I wish. In the event of retirement, I will not suffer a sanction or loss of rights to health or academic care.
- I authorize the responsible investigator and his collaborators to access and use the data obtained from my evaluations for the purposes of this research.
- I declare that I am over 18 years of age and wish to participate as a voluntary subject in this research. **Check** YES or NO.
- I declare that I do not have any chronic non-communicable diseases (chronic respiratory diseases, cancer, uncontrolled high blood pressure, diabetes, cardiovascular disease or other) and do not consume antidepressant, psychostimulant or antipsychotic medications such as Imipramine, bupropion, clozapine, benzodiazepines, in addition to having no history of epilepsy/seizure, history of stroke, traumatic brain injury, brain surgery, cochlear iron implants and pacemakers, severe headaches, severe depression, drug-alcohol abuse, not being pregnant or breastfeeding, that I am not under kinesic treatment, nor sports training systematically for 3 months. **Check** YES or NO.

**SIGNATURES**

Voluntary: name, signature, RUT and date

Principal Investigator: Name, Signature, and Date

Supervisor: name, signature and date

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## 12 DECLARATION OF CONSENT STUDY 2 (RESEARCHER'S COPY)

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