Brain and Pain: Understanding the central mechanisms of pain to improve management of patients with refractory chronic pain

Research centre and investigator details:

Research institution: Universidade de Santiago de Compostela

Research centre: Brain and Pain research group (BaP)

Address line: Campus Vida, Calle Xosé María Suárez Núñez, s/n, 15782

City: Santiago de Compostela

Postcode: 15705

Country: Spain

Principal researcher: Carrillo de la Peña, María Teresa

Collaborating researchers: González Villar, Alberto; Sanmartín Veiga, Noelia; Fernández Feijoó, Fátima; Vázquez Millán, J. Antonio; Gil Ugidos, Antonio; Carceller Ruiz, José Javier; López País, Pablo; Mayo Moldes, Mónica.

Contact emails: mteresa.carrillo@usc.es and joseantonio.vazquez.millan@rai.usc.es

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1. Justification of the project and theorical framework

Chronic pain is one of the most important public health priorities of the 21st century (Langley et al., 2011; Dueñas et al., 2015). It is estimated that about 19-25% of adult Europeans suffer from chronic pain of moderate to severe intensity, with increased prevalence as population ages (Breivik et al., 2006). Management of chronic pain implies an enormous economic burden for public health systems, and continues to be a challenge for healthcare providers, due to the inefficacy of current treatments (Leadley et al., 2012).

Conventional management of chronic pain is based on a combination of pharmacological and non-pharmacological therapies including oral nonsteroidal, anti-inflammatory drugs, intra-articular injections, physical therapy and opioid analgesics (Hochberg et al., 2012; Chaparro et al., 2014). However, these options have only demonstrated a partial efficacy and their benefits usually decrease over time (due to therapy tolerance, disease progression, and/or neural sensitization of pain-related neural structures), in addition to the adverse effects which accompany these therapies and counteract their benefits (Reinecke et al., 2015).

Refractory, pharmaco-resistant patients are a challenge for multiple medical departments, and it becomes necessary to consider alternative strategies (Leadley et al., 2012). To do so, we propose a shift from a disease-oriented to a mechanism-based management strategy of chronic pain. Chronic pain is a complex sensory and emotional experience that varies widely among people, depending on the context, individual construct of pain, and physiological state (Bushnell et al., 2013). It is defined as a persistent (lasting beyond 3 months) and maladaptive response, without the protective function of acute nociceptive pain (Treede et al., 2015; Merskey & Bogduk, 2012).

Although chronic pain diseases are very heterogeneous in terms of aetiology and clinical manifestations, they may share similar pathophysiological mechanisms related to the processing and inhibition of pain. Thus, multiple studies confirm that chronic pain sufferers tend to present a pattern of increased excitability to pain, and limited central analgesic regulation relative to healthy controls (Staud et al., 2008; Potvin & Marchand, 2016; Kosek & Ordeberg, 2000).

Therefore, constructing a mechanism-based management strategy of chronic pain requires to find techniques which target the brain processing of nociceptive signals and the central nervous dysfunctions present at chronic pain patients (Macfarlane et al., 2017).

In this vein, non-invasive brain stimulation (NIBS) techniques have become the forefront of novel experimental treatments of chronic pain. Those techniques have proved to be capable of modulating brain activity without surgical interventions and offer new methods to modulate pain-related brain activity in order to reduce pain suffering (Zortea et al., 2019), thus becoming an interesting alternative to traditional therapeutic approaches.

One of these techniques for brain stimulation is the **transcranial Electrical Stimulation** (tES). By applying a low current over the motor cortex through the scalp, this technique can excite or inhibit the neural activity, thus modulating brain processes like pain perception (Nitsche & Paulus, 2000; Nitsche et al., 2008). The most frequently used tES technique is **transcranial Direct Current Stimulation** (tDCS). It consists of the application of a constant low-intensity current (1-2 mA) usually through 2 electrodes (anode and cathode) placed on the scalp. This stimulation induces relatively sustained changes in cortical excitability and neuroplasticity (Paulus, 2003). More recently, **transcranial Alternating Current Stimulation** (tACS) has been used to modify cortical functioning (Fröhlich et al., 2015).

Transcranial electrical stimulation may be a key component for correcting defective central pain generating mechanisms. tDCS has been suggested to induce anti-nociceptive effects on experimental pain and have pain-relieving effect in different clinical conditions, using anodal stimulation over the precentral region contralateral to pain (Santos-Portilla et al., 2013). Although different cortical brain targets have been tested, the stimulation of primary motor cortex (M1) appears the most effective cortical target in chronic pain patients and their clinical improvements last beyond the time stimulation, probably due to solid neuroplastic modifications (Lima & Fregni, 2008). This finding is consistent with the hypothesis that cortical networks play a key role in pain processing and that the primary motor cortex (M1) may be a gateway to deep pain-related networks such as the thalamic nuclei and the cingulate gyrus (Baliki et al., 2008; Maarrawi et al., 2007). Evidence for pain reduction through M1 tDCS has been reported for chronic pain manifestations as diverse as pelvic pain, spinal cord pain, cancer, diabetic neuropathy, low-back pain, temporomandibular disorders, and migraine, among others (Lefaucheur, 2016).

Transcranial electric stimulation (tES) has several advantages: it is portable, non-invasive, engineered from low-cost components, has minimal adverse effects, is well

tolerated, easy to use, and multiple animal and clinical studies confirm its safety at low intensities. Recently, a compendium of experts on tDCS released a review covering more than 18,000 stimulation sessions (≈8,000 patients) in which no significant adverse events were reported for multiple populations (Antal et al., 2017).

Nevertheless, there are some gaps in this field. First, the evidence of its efficacy for pain relief is still limited, as recent Cochrane reviews on the effectiveness of tDCS in chronic pain concluded that the evidence available is not solid enough (O'Conell et al., 2014; 2018). Most current studies still have significant biases (not blinded or placebo-controlled), poor methodological quality (insufficient number of sessions, no follow-ups) and small sample sizes.

Second, previous studies have exclusively focused in tDCS, without paying attention to tACS. In the unique previous clinical trial with chronic low back pain patients, Ahn et al. (2019) found significant correlation between alpha power and pain. Interestingly, stimulation with tACS significantly enhanced alpha oscillations in the somatosensory region, and this increase was correlated with pain relief. Therefore, tACS demonstrate having the potential to relief pain, but it also can help to clarify the mechanism by which tES can modify cortical networks involved in pain (Woods et al., 2016; Peng & Tang, 2016).

Furthermore, no alternatives to the hospital delivery of this treatment have been explored. Although the tES equipment can be controlled remotely and thus allows home-based interventions. At-home interventions are positively perceived by the patients, as they reduce the time involved in treatment and visits to medical centres, favouring self-management of the disease and reducing the burden on family members; also, they increase the efficiency of the professionals, who can attend several patients at the same time.

As we stated before, we are particularly interested in delving into the pathophysiological mechanisms which are associated with chronic pain. Therefore, this clinical trial aims to evaluate the changes in these mechanisms due to the treatment with transcranial electrical stimulation. To this end, we will use two quantitative sensory tests (QST) to assess central nervous dysfunctions in processing and inhibition of pain in clinical population, namely Conditioned Pain modulation (CPM) and Temporal Summation of Second Pain (TSSP).

Conditioned Pain Modulation consists of the reduction of the pain provoked by a given noxious stimulus (i.e., test stimulus) when another painful stimulus (i.e., conditioning stimulus) is applied to a remote area (i.e., pain inhibits pain; Yarnitsky et al., 2010; Willer et al., 1984); whereas TSSP occurs when repeated noxious stimuli over the same corporal area amplifies pain sensations, probably due to a central sensitization derived from the enhanced response of dorsal horn neurons to repetitive nociceptive signals from C-fibers (Dickenson, 1997). Concerning CPM response, approximately 70% of chronic pain patients display a large and statistically significant reduction in their pain inhibition system relative to healthy controls, as evidenced in a meta-analysis by Lewis et al (2012). At the same time, various studies have found greater TSSP in chronic pain patients relative to healthy controls (Staud et al., 2001; Arendt-Nielsen et al., 2010; Petersen et al., 2015)

Altogether, the existing evidence supports that both CPM and TSSP could act as biomarkers of endogenous pain modulation to distinguish chronic pain patients. In fact, the efficiency of these endogenous modulatory pain systems could serve as a predictor of treatment outcomes with tES.

Lastly, the study of brain electrical activity recordings (EEG) in resting state and in response to noxious stimuli may also help to characterize the brain processing of nociceptive stimuli and how these signals are amplified or mitigated (González-Villar et al., 2019). For this reason, another purpose of this research is to evaluate the changes in neural patterns which occurred in chronic pain patients after transcranial electrical stimulation treatment. Specifically, we purport to make a time-frequency and connectivity analysis of the EEG paying special attention to those key frequency bands involved in nociceptive perception (Hu et al., 2013; Liberati et al., 2017; Fallon et al., 2018), namely Theta (≈4-7 Hz), Alpha (≈8-12 Hz) and Gamma (≈35-70 Hz). Brain activity will be recorded both in resting-state (Fallon et al., 2016; Choe et al., 2018) and in response to painful heat and cold stimulation (De Keyser et al., 2018; De Tomasso et al., 2014, 2017).

2. Objectives and hypothesis

The main objective of this clinical trial is to test the efficacy of two different transcranial electrical stimulation techniques (tES) to modify dysfunction of central modulatory mechanisms of pain, and to improve symptoms and quality of life in refractory chronic pain patients.

In this vein, we hypothesize that transcranial electrical stimulation procedures will be more effective than sham to improve pain and related symptoms. Besides, central biomarkers of pain processing and modulation (i.e., CPM, TSSP and EEG) will be useful to predict the patient response to treatment and thus, the efficacy of these tES procedures.

Based in these principal ideas, we propose the following secondary or specific objectives:

A. To analyse the relationship between the studied biomarkers and clinical pain characteristics of patients (intensity, location, frequency, duration, daily interference caused by pain).

B. To stratify patients and propose profiles based on the selected biomarkers, which may be useful to improve diagnosis and to guide individualized treatment plans.

C. To develop home-based treatment schemes for patients with refractory chronic pain. We will assess if tES procedures are safe, feasible and acceptable for the at-home management of this medical condition.

D. To test if tES techniques are self-manageable by patients and to observe the impact of this treatment in the caregiver-burden declared by the reference person.

E. To test the efficacy of tDCS (Direct current) versus tACS (Alternant current) to modify dysfunction of central endogenous analgesia (i.e., CPM and TSSP) and to reduce pain and related symptoms in the patients, in a placebo-controlled clinical trial.

F. To analyze how the different tES techniques (tDCS and tACS) affect brain oscillatory activity, and to test if the changes in oscillatory activity are related to pain relief.

G. To test the power of the biomarkers/patients' stratification to predict treatment efficacy and to identify the characteristic of best responders patients.

H. To assess the effect of sex/gender and other modulator variables (age, disease duration, medication, lifestyle, mood…) on all the analyses (central biomarkers, patients' stratification, response to treatment…).

3. Study design

The research is classified as a double-blinded, randomized clinical trial with one control group which receive a sham stimulation.

The transcranial electrical stimulation intervention is considered the independent variable, which contains three different conditions or categories differentiated by the type of stimulation used. These conditions define the three groups of treatment:

1) Transcranial direct current stimulation (tDCS), which induces a continuous current over the left primary motor cortex (M1). Current intensity is set at 2mA and it is applied for 20 minutes, with ramp-up and ramp-down of 15 seconds at the beginning and end of the stimulation period.

2) Transcranial alternat current stimulation (tACS), which induces an alternant current over somatosensory cortical region. Current intensity is set at 10-Hz and it is applied for 20 minutes, with ramp-up and ramp-down of 15 seconds at the beginning and end of the stimulation period.

3) Sham stimulation, which acts as a placebo-control group. It uses the same montage as the previous ones, but it does not emit any kind of current. The position of electrodes will be similar to the previous conditions, but the current will be just activated during the ramp-up and ramp-down moments.

Chronic pain patients are randomly assigned to one of these groups, although the active stimulation conditions agglutinate the 80% of sample (40% tDCS; 40% tACS), whereas the control group contains by the remaining 20%.

As dependent variables, we consider the assessed clinical symptoms, mainly pain characteristics (including intensity, location, frequency, duration and daily interference caused by pain), fatigue, depression/anxiety, sleep quality, physical functioning and life quality, following the guidelines proposed by the *Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials* (IMMPACT; Dworkin et al., 2005).

Besides, as far as we aim to assess the efficacy of tES techniques to restore the potential dysfunctions in processing and modulation of pain in patients, central biomarkers as Conditioned Pain Modulation (CPM), Temporal Summation of Second Pain (TSSP) and EEG are also included as dependant variables. Thus, we try to identify any change in these variables which could be attributable to the intervention.

The intervention and evaluation protocols are more in-depth defined in the following sections.

4. Sample and recruitment

For planning the sample size for this research, we used Gpower (v.3.1.9.2) software. Sample size was estimated for repeated measures ANOVA with three groups (tDCS, tACS, Sham) and two measurements (pre-treatment vs. post-treatment). Statistical power (SP) was predetermined a priori with a value of SP=0.99 (α=0,01) to increase the validity of the subsequent analysis and ensure that we do not miss any statistically significant result.

We based the calculation on the data extracted from the meta-analysis by Zortea et al. (2019), who reported a moderate effect size for reduction of pain levels (F=0.68) in chronic non-cancer pain patients using the tDCS montage stimulating M1. These results were obtained after comparing 380 patients receiving active tDCS versus 381 who were given Sham stimulation.

Assuming this moderate effect size and the rest of described parameters (SP=0,99), a total of 21 patients would be large enough to detect statistically significant changes in the whole sample. However, it cannot be ignored the non-despicable drop-out rates of this patient profile, corroborated by the own researchers in previous investigations. Besides, we are interested in assessing the effect size of the tDCS intervention among the different categories or types of chronic pain, just as defined by the ICD-11 (Treede et al., 2015), and that requires to create big enough comparable groups. For these reasons, we decided to recruit a larger number of participants, thus stablishing the sample size in 120 patients with refractory chronic pain.

Concerning this research, pain is defined as refractory, regardless of etiology, when it meets the two following conditions. First, multiple evidence-based biomedical therapies

used in a clinically appropriate and acceptable fashion have failed to reach treatment goals that may include adequate pain reduction and/or improvement in daily functioning or have resulted in intolerable adverse effects. Second, pain persists even after psychiatric disorders and psychosocial factors that could be influencing treatment outcomes have been assessed and appropriately addressed.

Epidemiological studies have consistently reported higher prevalence rates of chronic pain syndromes among women, compared to men (Jiménez-Trujillo et al., 2019; Cimas et al., 2018). As we intend to create a feasible and useful tool for clinical practice, these gender differences must also be considered when designing the recruitment plan and deciding the sex distribution of the sample. As we aim to assess the influence of sex/gender in tDCS treatment efficacy and central pain modulation mechanisms, we will recruit both male and female patients, although the latter will represent about 70% of the total sample, in accordance with clinical reality; whereas males will represent at least the 30% of the selected patients, in order to improve and facilitate subsequent comparative analysis. The **inclusion criteria** applied for the selection of patients are the following:

- Suffering a chronic pain condition of non-cancer nature. Those patients who report chronic pain even after overcoming an oncological process are suitable to participate, but only if they have received the definitive medical discharge and have been free from radiotherapy/chemotherapy for at least twelve months.
- Adult subjects (18-65 years old).
- Subjects able to provide informed consent to participate in the study and to self-report pain.
- Existing chronic pain which reaches an intensity of at least 4 on a 0-10 Numeric Rating Scale (NRS) on average over the past 3 months prior to enrolment.
- Pain intensity of at least 5 on a 0-10 NRS over the week prior to enrolment.
- Diagnosis of pharmaco-resistance to analgesic drugs across the WHO ladder.

Participants are allowed to continue with their usual pharmacological regimen, but it must have been stable during the two months previous to the enrolment, and it must not suffer modifications during the whole research period. We will account for the potential effects of some drugs over the efficacy of tDCS/tACS treatment (McLaren et al., 2017), making a registry of patients pharmacological prescriptions to consider them in further

analysis. Rejecting patients who consume medicaments which can apparently interfere with tDCS/tACS effects would not be a well-balanced alternative and would result in a huge loss of participants, since some of these drugs are included as priority treatment for many chronic pain conditions. As far as the **exclusion criteria** are concerned, they are exposed below:

- Chronic pain derived from current cancer disease.
- Pregnant women or women in fertile age not having efficacious contraception during the whole period of the study.
- History of alcohol or drug abuse within the past 6 months as self-reported.
- Suffering from unstable medical conditions (e.g., uncontrolled diabetes, uncompensated cardiac issues, heart failure or chronic obstructive pulmonary disease).
- Intracranial ferromagnetic devices or implanted stimulator (pacemaker, basal ganglia stimulator, vagus nerve stimulation).
- Antecedents of, or active epilepsy.
- History of neurosurgery, psychiatric diseases other than anxiety or depression, traumatic brain injury with loss of consciousness, and/or cortical lesions.

For recruitment phase, we count on the collaboration of three physicians from the Public Health System who work in regional specialized units for the treatment of pain. They will inform those patients who match the inclusion criteria about the existence and nature of the research, offering them the possibility of participating in. Patients who show interest are required to sign an initial consent which allows principal researchers to get in touch with them by telephone. At that moment, patients will be given a more in-depth explanation about the clinical intervention and their implications; researchers will also check that the patient comply with inclusion criteria and he/she does not meet any exclusion criteria.

Those patients who agree to receive the treatment are summoned to a face-to-face session at the research group laboratory. At this stage, patients must sign the informed consent to participate in the research and right after the pre-evaluation protocol is implemented.

In another vein, this research also seeks to determine whether the home-based treatment approach is feasible to be applied by patients themselves and how it affects to the caregiving workload for the reference person[1]. To this end, in the initial phone call patients will be asked for identifying that caregiver figure in their own life, in case it effectively exists. Caregiver is defined as the person who worries about the patient's health condition, helps them in daily chores and, in sum, is in charge of covering their emotional and material needs (Bookman & Harrington, 2007).

Identified caregivers are invited to a brief face-to-face interview to evaluate their burden and health status. Given the exploratory character of this purpose, we do not set a priori sample size for caregivers, although the question about the caregiver will be formulates to all the patients.

5. Description of the treatment

Home-based transcranial electrical stimulation device consists of a custom headgear with fixed electrode sites and built-in cabling made for a simplistic setup for tDCS/tACS stimulation. Systems are equipped with strict dose control feature that provide reliable control over the intensity and timing of stimulation, turning these devices into a feasible and safe clinical alternative.

The equipment is specifically designed for easy and simplistic self-setup and allows the researchers to remotely check the position of electrodes and also monitor the stimulation session. This is possible because the devices have an Internet wireless connection and send the data obtained to an online platform, only accessible to the principal researchers.

From pre-stimulation set-up, to during stimulation monitoring, to post-stimulation confirmation, the device provides an intuitive and clear indication of electrode contact quality, facilitating the proper adjustments to ensure a successful stimulation. In case stimulation is aborted or interrupted, impedance is abnormal, or other faults are detected, the system will automatically abort or alter stimulation and the incident details stored. This system also allows researchers to supervise the treatment compliance.

[1] It must not be overlooked that patients with chronic pain can find difficulties/limitations to accomplish the basic daily tasks and thereby be partially dependant (Meulders, 2019; Zale et al., 2013)

Besides, these devices uses a software which allows a double-blinded procedure. Nor the researchers neither the participants will know what kind of stimulation is receiving each of them.

The intervention plan comprises fifteen stimulation sessions applied with a daily frequency during an uninterrupted period of time which convers just over two weeks. Thus, sessions will be scheduled for each patient before the beginning of the treatment, arranging with the patient the hour frame for stimulation. Stimulation parameters/sites for each condition will be as follows:

- Transcranial direct current stimulation (tDCS). Current intensity of 2mA applied during 20 minutes at the left M1, with anodal electrode placed in C3 and cathodal in FP2, following the International 10-20 EEG System. Ramp-up and ramp-down comprises 15 seconds at the beginning and end of the stimulation period.
- Transcranial alternant current stimulation (tACS). Following the design stablished by previous studies (Ahn et al., 2019), two electrodes will be placed at F3 and F4 and connected together for 10-Hz tACS (or the frequency which shows best sensitivity or specific), and one electrode at Pz will be the return electrode. This setting is used to stimulate the somatosensory cortical region. Stimulation will last for 20 minutes, with a ramp-up and ramp-down of 15 seconds at the beginning and end of the session.
- Sham stimulation. The electrode montage will be either the tDCS (for half of the participants) or the tACS montage (for the other half), and we will just apply the current at the ramps terms, but no current in the interval between the ramps which practically comprises the whole session.

At the second pre-treatment evaluation session, patients will receive the portable stimulator with the properly explanations about its functioning. It is planned to make a training stimulation session during this visit to ensure that patients are able to connect and manage the device.

6. Evaluation protocol and follow-up

6.1. Evaluation phases

Regarding the evaluation protocol, pre-treatment assessment is divided in two different sessions, separated by two weeks.

After obtaining their contact number from physicians, researchers maintain a first phone talk with the proposed participants to ensure they not comply with any exclusion criterion. During this brief interview, the first meeting with patients is also scheduled, according to their availability.

The first face-to-face session is intended to initiate the pre-evaluation process and it takes place fifteen days before starting the treatment. After signing the informed consent, participants will complete an exhaustive assessment protocol which includes an interview about their health status and clinical history, a set of quantitative sensory tests (Pain thresholds, CPM, TSSP) and some other questionnaires to assess psychosocial variables.

From this point to the end of the post-treatment evaluation, patients are required to complete a daily online survey about their symptoms and health condition. Moreover, patients will be given a wristband actigraph which should wear during the whole research period (except follow-up), in order to monitor their physical activity and sleep patterns.

The next evaluation will take place two weeks after the first one. During this period, participants are required to complete a daily online survey about their symptoms and health condition. Moreover, they are given a wristband actigraph which allows to monitor their physical activity and sleep patterns.

At the second session, patients will complete electroencephalographic records in different conditions and tasks, some of which include painful stimuli. Furthermore, we will collect additional clinical features through validated questionnaires and may also repeat the quantitative sensory testing. Caregivers of chronic pain patients will also be invited to this appointment to maintain an interview with researchers, which aims to determine their health status and the stress-related to the caring tasks.

Finally, researchers will give the participants the portable stimulator to apply the tDCS/tACS treatment, with the properly explanations about its functioning. It is planned to make a training stimulation session during this visit to ensure that patients are able to

connect and manage the device; researchers will also be available to make a video-call to assist the participant in the first stimulation session.

After completing the treatment period, participants are summoned to other two evaluation sessions with the same structure and assessment tools as in pre-treatment phase; in case of the daily measurements, the comparison is made between the average of the pre-treatment period and that of the post-treatment period. Therefore, differences observed between these two time-measurements are considered as index of the treatment efficacy. At the post-evaluation session, participants will also answer some questions about the satisfaction with the treatment and self-perceived usefulness/improvement.

Finally, in order to assess the long-term improvement derived from tES, we will contact participants by phone in order to invite them to a follow-up session six months after finishing the treatment. All questionnaires and sensory tests will be applied in the same way, except for daily numerical rating scale. Differences between these results and those obtained in pre-evaluation and post-evaluation will be analysed.

6.2. Evaluation methods and assessment tools

The following section provides a more in-depth description about the methodology used to evaluate the patients and their characteristics. The assessment process includes a compendium of questionnaires about clinical and psychosocial characteristics, several quantitative sensory tests and EEG records in diverse conditions.

Regarding the first face-to-face session, we collect relevant sociodemographic data to characterize the sample (e.g., sex, age, occupation, dependency certificate), which does not enable to know the personal identity. The interviewers also inquire about medication and lifestyle questions, such as smoking, alcohol consumption, drug use and physical activity. Patients may also be requested to execute some short physical tasks (for example, *Stais Climb Test*) to obtain a performance-based index of their physical function (Dobson et al., 2013). We also question about the type and onset of chronic pain, and whether he/she has been diagnosed with other relevant medical or psychiatric conditions.

Clinical features and health condition are assessed using the translated version of reliable and validated questionnaires for Spanish chronic pain population. At this initial stage, we focus on assessing relatively stable measures:

- Multidimensional Pain Inventory (MPI; Kerns et al., 1985; Pastor et al., 1995). It serves as a general index about the severity of the disease by asking for pain intensity, daily interference, self-perceived control over pain and perceived support from significant others.
- Short Form Health Survey SF-36 (Vilagut et al. 2005). World widely used, this questionnaire provides a complete picture of the participant health state, including subscales about vitality, mental health and physical, emotional and social functioning, among others.

We will also perform the quantitative sensory testing, which consists of the pain thresholds and the above-mentioned procedures to assess abnormalities in endogenous modulatory pain mechanisms, namely Conditioned Pain Modulation (CPM) and Temporal Summation (TSSP).

Pain thresholds are defined as the minimum intensity which must reach a stimulus to become in painful, as perceived and reported by the own person. Pressure pain threshold will be calculated using a digital handhold algometer (Wager Force One Model) which puts progressively heavier pressure over the skin surface. Heat pain threshold is obtained with a computerized thermal stimulator which progressively enhances the temperature of the skin with a small contact metal plate. In both cases, pressure and temperature increases to a constant pre-fixed rate, until the participant press a button to indicate she/he starts to feel pain. Pressure pain threshold is measured in kPa, whereas heat pain threshold is stablished as the temperature in degrees Celsius.

Although the specific CPM and TSSP protocols are not completely defined yet, we count with a wide catalogue of usually used instruments and equipment to perform these tests (Fernandes et al., 2019; O'Brien et al., 2018)

Conditioned Pain Modulation requires of two different painful stimuli applied in heterotopic body areas; thus, the conditioning stimuli (CS), tonic in nature, reduces the pain sensations from the phasic test stimuli (TS). As CS, we will use the ischemic pain produced by pressure cuff and/or the cold pressor test, which means the participant have to immerse their non-dominant hand into cold water. Regarding TS, we opt for the same procedures as to calculate the pain thresholds (i.e., digital handhold algometer and thermal stimulator), given that we aim to compare these isolated thresholds with those obtained

while the CS is present. The difference between these two measures is stablished as the CPM index.

Tentatively, Temporal Summation of Second Pain (TSSP) will be evoked with the thermal stimulator. After stablishing the parameters which corresponds to a medium pain level (5/10 NRS) for each participant, it will be applied ten repetitive pulses with that temperature over the skin, separated by two and a half seconds. Patients have to rate the pain intensity which produces the first, fifth and last stimuli. The difference in pain intensity between the first and last pulse is stablished as the TSSP index.

Finally, we will explain the daily assessment plan to patients, which starts at this point (i.e., fifteen days before the treatment onset) and continues until fifteen days after the stimulation sessions have finished. Every day during this period, participants will be requested to complete a brief online survey to track the intensity of their symptoms and obtain a more reliable measure. These questionnaires will be sent to patients by phone message, after getting permission from participants.

Specifically, the daily survey consists of several Numerical Rating Scales (NRS) of eleven points (0-10) which ask about the intensity and unpleasantness of pain, interference, fatigue and medication usage, among others. During treatment period, participants can also report any side effect of stimulation through these questionnaires. For each symptom, we will obtain an average of measures obtained before starting the treatment, other average with measures during the treatment and one last average for post-treatment phase (e.g., fifteen days after finishing the intervention).

Moreover, patients will be given a wristband actigraph which should wear during the whole research period. These devices are capable of detecting the sedentary and activity bouts, as well as the intensity of these last ones, the raw acceleration and the distance walked every day. Besides, actigraphs can also measure the total sleep time, the sleep latency and the awakenings after sleep onset. Thanks to this actigraphy technology, physical functioning and sleep patterns will be effectively daily evaluated.

Thus, by the day of the second evaluation session, we will have already obtained a set of daily measures whose average will serve as a reliable clinical baseline. In this second appointment, as part of the potential biomarkers of chronic pain, we will register the electroencephalography (EEG) of the patients during various conditions (Davis et al., 2017). Firstly, EEG will be assessed during a resting state to capture spontaneous brain

activity, the spectral power of the oscillations and inter-site phase connectivity (Ploner et al., 2017). Secondly, we will analyse wave components of the contact heat evoked potentials (CHEPs) to obtain a neural correlate of the painful stimuli processing. For last, in order to study the modulatory role of attention in pain perception, we propose to obtain the evoked potential derived from a TSSP protocol, both paying exclusive attention to pain and during a simple cognitive task.

Besides, we will repeat the same procedure of quantitative sensory testing to ascertain its reliability. Finally, the following questionnaires will be used to get an accurate measure of some key symptoms and problems which usually accompanies chronic pain:

- Hospital Anxiety and Depression Scale (HADS; Cabrera et al., 2015). It represents a really useful tool to assess mood state and screen for depressive or anxiety disorders, which frequently cooccurs with chronic pain.
- Modified Fatigue Impact Scale (MFIS; Duarte et al., 2017; Kos et al., 2005), which accounts for the physical, emotional and social components of fatigue. Fatigue usually accompanies chronic pain conditions and results in great limitations for the daily functioning of patients.
- Pittsburgh Sleep Quality Index (PSQI; Macías & Royuela, 1996). This inventory inquiries into several areas about the sleep patterns, such as the related disorders, the self-perceived quality or the time passed until falling asleep.
- Zarit Burden Interview (Martín et al., 1996). This instrument is used with the principal caregivers of the patients to assess the stress and negative feelings associated with the caring tasks. Thus, it represents the core of the evaluation protocol for caregiver, and it intends to pay attention to this figure but also to add information about the patient autonomy.

In sum, all the proposed questionnaires assess relevant clinical variables which are expected to be improved by tES treatment. Therefore, changes observed in them between pre- and post-evaluation will be subjected to statistical analysis and taken as efficacy indices of treatment.

However, there are some other variables which, despite not expecting to be modified, could influence the treatment outcomes for better or worse. We refer to social support, self-perceived stress, catastrophizing thinking and beliefs about controllability of pain

(Adams & Turk, 2015; Keefe et al., 2004; Jensen et al., 2011). Thus, these factors must be taken into account when assessing the efficacy of tES intervention and we intend to account them as covariates in statistical analysis.

Changes observed in criteria variables between pre- and post-evaluation must be equal or higher than the 30%, in order to ensure their clinical significance. It means that the improvement observed in self-reported questionnaires and in sensory testing (except for EEG) have to achieve or surpass the 30% of the original outcome. The direction of these differences depends on the specific scale; for example, it is expected a reduction in the global MPI score after treatment, but also a rise in pain thresholds. In the case of EEG, the analysis pre-post treatment are only subjected to the statistical significance. However, changes in brain activity patterns attributed to the tES will be tried to relate with improvement in clinical features.

Although all explained measurements are considered as success criteria of treatment, we selected pain intensity as the primary end point, taken as the average obtained from daily numerical rating scale. In this sense, participants will be classified into responders when they report, at least, a 30% decrease in their pain intensity. The rest of the variables are taken as secondary end points and are also regarded as treatment-efficacy indexes, basically the pain thresholds, life quality, physical functioning, interference caused by pain, pain unpleasantness, sleep quality, depression/anxiety, fatigue, caregiver burden and CPM/TSSP responses.

Table 1: End points of the clinical trial and their respective evaluation instruments

End points		**Assessment tools**
Primary end point	Pain intensity	Numerical Rating Scale of eleven points (0-10 NRS). Average obtained from daily self-reports during the fifteen days before treatment and the fifteen days after treatment.
Secondary end points	Global severity of chronic pain syndrome	Global and subscales scores of Multidimensional Pain Inventory (MPI).
	Interference caused by pain in daily living	Subscale score of Multidimensional Pain Inventory (MPI). Numerical Rating Scale of eleven points (0-10 NRS). Average obtained from daily self-reports during the fifteen days before treatment and the fifteen days after treatment.
	Pain thresholds	Pressure pain threshold using a digital handheld algometer, measured in kPa. Heat pain threshold using thermal stimulator, measured in degrees Celsius.
	Life quality	Short Form Health Survey SF-36
	Physical functioning	Daily recorded physical activity using actigraphy technology. Subscales scores of Multidimensional Pain Inventory (MPI)
	Sleep quality	Pittsburgh Sleep Quality Index (PSQI)

		Daily recorded sleep quality using actigraphy technology.
	Pain unpleasantness	Numerical Rating Scale of eleven points (0-10 NRS). Average obtained from daily self-reports during the fifteen days before treatment and the fifteen days after treatment.
	Mood and emotional functioning	Hospital Anxiety and Depression Scale (HADS) Numerical Rating Scale of eleven points (0-10 NRS) for assessing daily anxiety. Average obtained from daily self-reports during the fifteen days before treatment and the fifteen days after treatment.
	Fatigue	Modified Fatigue Impact Scale (MFIS) Numerical Rating Scale of eleven points (0-10 NRS). Average obtained from daily self-reports during the fifteen days before treatment and the fifteen days after treatment.
	Caregiver burden	Zarit Burden Interview (ZBI) applied to the identified reference person in charge of caring the patient
	Endogenous pain inhibition response	Score obtained from Conditioned Pain Modulation (CPM) procedure
	Endogenous pain facilitation response	Score obtained from Temporal Summation of Second Pain (TSSP) procedure

	Global satisfaction with treatment and self-perceived improvement	*Ad-hoc* designed questionnaire

7. Data analysis plan

First of all, we will perform reliability analysis on sensory measures, such as pain thresholds, CPM and TSSP magnitudes. The Intraclass Correlation Coefficient to stablish the degree of association and agreement among the two scores obtained for each test.

After applying the pertinent filters to EEG records and once the descriptive analyses of the sample have been done, we will observe the correlation of the CPM/TSSP response and the EEG registry with the clinical features of the sample, taking into account just the pre-treatment evaluation. In order to reinforce the results, we may add *Linear regression analysis* to verify whether the dysfunctions in central modulatory mechanisms and brain processing of painful stimulus (CPM, TSSP, EEG) can act as predictors of the symptoms severity of chronic pain patients.

Besides, we will conduct simple ANOVA analyses to compare these indexes of pain processing and modulation (CPM, TSSP, EEG) between specific groups of patients, divided by type/origin of chronic pain and sex. We reserve the possibility of making *Cluster analyses* in the basis of the mentioned central biomarkers, following by an ANOVA comparison of clinical features between the emerged groups.

Besides, participants will be classified into CPM and TSSP respondents or no-respondents taking into account their results in these sensory tests. Those patients who report a significant increment in pain thresholds will be considered respondents; whereas the opposite applies for TSSP, as it must be detected a significant increasement in perceived pain intensity in the last pulse compared to the first one. Depending on the proportions observed, it could be useful to divide TSSP respondents based on the degree of the pain sensitization. Regarding this sample division, we can compare the clinical profile of respondents and non-respondents patients using *Chi square statistic*.

As far as intervention efficacy is concerned, qualitative analyses will focus on differentiating the patients who effectively respond to treatment (Treatment-respondents) from those who do not improve (Non-treatment-respondent). Respondents are those

participants whose improvement in a certain clinical variable are equal or higher than the 30%; whereas non-respondents are all those who do not comply with this criterion. This variation is extracted from the comparison of pre- and post-treatment measurements.

Therefore, for each of the endpoints, we will obtain a number/percentage of respondents and non-respondents. Using the *Chi-square test*, we will compare the proportion of respondents between treatment groups to identify the most efficacious stimulation procedure. A separated analysis will be done for each described endpoint, which define what a respondent is.

The main quantitative statistical analyses to assess the efficacy of transcranial electrical stimulation techniques consist of ANOVA-tests of repeated measures with three groups. Time-measures for each of the above-mentioned endpoints are taken as intragroup variables (pre vs. post), whereas intergroup measures refer to the received stimulation or treatment (tDCS vs. tACS vs. Sham). Thus, both clinical variables (for example, pain intensity, fatigue, sleep quality, disease severity and interference) and potential biomarkers (including brain oscillatory activity registered by EEG, CPM and TSSP response) are considered as intragroup variables.

Those covariates which show a significant correlation with clinical outcomes will be also included in their correspondent ANOVA analysis. These potential covariates are basically age, self-perceived stress, social support, catastrophism and medication intake.

All these statistical analyses will be repeated in separated groups of patients, created in the basis of sex, type and duration of chronic pain, among other characteristics. The objective is to assess whether the clinical outcomes depend on sex or diagnosis, as each tES could be more effective for specific diseases.

CPM/TSSP response and EEG pattern observed before the tES application are also regarded as potential predictors of the treatment efficacy. Thus, the pre-treatment indexes of these biomarkers will be used as independent variables in *Linear regression models*, which includes the clinical improvement in each endpoint as dependent measure. The procedure will be repeated with *Logistic regression analysis* stablishing the respondent vs. no-respondent categories as dichotomic variable.

For last, we will register and assess the percentage of dropouts with their respective motives, in order to obtain an index of the feasibility of home-based tES approach. Client

satisfaction index and caregiver interview will also include questions about the capability of participants to manage with tES devices, data which will be qualitatively analysed.

8. Chronogram

WORKING PLAN (WP) TASK \ MONTH		3	6	9	12	15	18	21	24	27	30	33	36
WP1. Development and selection of assessment and monitoring tools for refractory chronic pain patients													
Task 1.1.	Review of the literature and identification of the most common and important variables used as outcomes in clinical trials with chronic pain population.												
Task 1.2.	Selection of valid and reliable instrument to assess pain and the relevant clinical domains identified in the previous phase.												
Task 1.3.	Transfer of chosen instruments into a digital format to be applied through an electronic application to facilitate data collection and codification.												
Task 1.4.	Contact with technology companies and acquisition of portable tES equipment, actigraphy devices and stimulators for quantitative sensory testing.												
Task 1.5.	Review of the literature and definition of quantitative sensory tests (CPM/TSSP) and EEG protocols.												
Task 1.6.	Preparing of application and obtaining the Ethical Committee approval												
Task. 1.7.	Familiarization of researchers with purchased devices and conducting pilot tests to ensure their correct performance/operation.												
WP2. Recruitment and first evaluation of chronic refractory pain patients: Pre-treatment phase													
Task 2.1.	First contact and recruitment of participants by physicians from Public Health System.												
Task 2.2.	Telephone contact with participants to explain the nature of the project and arrange a face-to-face assessment session.												

Task 2.3.	First pre-treatment assessment session: Signing of informed consent, application of pre-selected questionnaires and sensory tests.												
Task 2.4.	Daily assessments of clinical variables during the fifteen days following pre-treatment assessment session using actigraphy technology and electronic surveys, remitted to patients through phone messages.												
Task 2.5.	Second pre-treatment assessment session: Application of pre-selected questionnaires, sensory tests and EEG registry. Delivery of tES devices and the correspondent explanation.												
WP3. Home-based treatment with tES for chronic refractory pain patients													
Task 3.1.	Daily Transcranial electrical stimulation sessions during fifteen consecutive days.												
Task 3.2.	Remote monitoring and compliance surveillance of the tES sessions from principal researchers.												
Task 3.3.	Daily assessments of clinical variables and side effects during treatment period using actigraphy technology and electronic surveys, remitted to patients through phone messages.												
WP4. Evaluation of the efficacy of tES intervention for chronic refractory pain patients: Post-treatment phase													
Task 4.1.	Post-treatment assessment session: Application of the same tests as in pre-treatment evaluation, adding satisfaction and self-perceived improvement scales; and devolution of tES devices.												
Task 4.2.	Daily assessments of clinical variables during the fifteen days following post-treatment assessment session using actigraphy technology and electronic surveys, remitted to patients through phone messages.												
Task 4.3.	Follow-up assessment session: Application of the same tests as in previous evaluations six months after finishing the tES treatment.												

WP5. Statistical analyses of the clinical trial data, discussion of results and writing of reports												
Task 5.1.	Data analysis of pre-treatment evaluation results: Pain processing and modulation indexes (CPM, TSSP, EEG) and correlations with clinical features of patients.											
Task 5.2.	Data analyses of immediate tES effects/outcomes and potential predictors of treatment efficacy.											
Task 5.3.	Data analyses of long-term tES effects/outcomes.											
Task 5.4.	Group discussions about the available results.											
Task 5.5.	Writing reports and dissemination of results for scientific community.											

9. Security and ethical-legal issues

We are committed to adhere to all relevant international, EU and national legislation and guidelines relating to the conduct of clinical studies. Since our research involves human samples, we will organize a preliminary seminar on ethics questions to guarantee respect for research participants and the appropriate behaviour of the involved researchers and clinicians in regard to the health and welfare of the participants.

The purchased transcranial electrical stimulation devices have obtained the CE Certificate for research use, and in some countries, for clinical use as an off-label treatment. This certificate warrants the compliance with European standards about the security offered by the equipment.

For research, in most countries, only IRB/Ethical Committee approval is required, since the studies using tDCS are considered to be of minimum risk, provided that the exclusion criteria are strictly applied (i.e., intracranial ferromagnetic devices or implanted stimulators; antecedents of, or active epilepsy; history of neurosurgery, traumatic brain injury with loss of consciousness, and/or cortical lesion). Researchers are committed with ascertaining that every single enrolled patient complies with all the inclusion criteria and he/she does not match the exclusion criteria, in order to ensure that there is no health condition or circumstance which advises against participating in the study.

As explained above, no significant adverse events have been reported by a comprehensive review covering more than 18.000 stimulation sessions and approximately 8.000 patients (Antal et al., 2017). Thus, at present, most IRB committees approve tDCS treatments based on the promising data already available, without major concerns or obstacles. At the time of uploading this document, we have already obtained the approval from the competent Ethical Committee (Research Ethical Committee of Santiago-Lugo; Registry Code: 2021/021).

This project is developed following the requirements of Helsinki Declaration (1964) and subsequent assembly ratifications (Tokyo, 1975; Venezia, 1983; Hong Kong, 1989; West Somerset, 1996; Scotland, 2000; Seoul, 2006; Fortaleza, 2013) about the ethical principles for medical investigations involving human beings; as well as the national-scope guidelines collected in the RD 1090/2015, about clinical trials and medical praxis.

As in any other randomized clinical trials, a percentage of participants will be assigned to a Sham condition. Patients will be aware about this fact before the start of the study although, as for the researchers, patients will not know which was their treatment group until the end of the trial. Given that participants will be randomly assigned to one of the groups, we guarantee that there is no discrimination based on gender, race, sexual orientation or any other individual characteristic. Besides, patients in the placebo group will continue to receive their regular treatment and, in addition, due to their participation in the study, will receive day-to-day attention on their health state evolution.

As far as the data processing is concerned, researchers will not ask for personal information which could reveal the identity of the patients, thus maintaining anonymity. We are committed to respect the European and national legislation about Personal Data Protection, whose highest authorities refers to the *Regulation (EU) 2016/670 of the European Parliament and of the Council, of 27 April 2016, on the Processing and Protection of Personal Data* and the Spanish law called *Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantías de los derechos digitales*.

The research centre is responsible for the data treatment and processing. Data collected will be exclusively used for the objectives described in this investigation protocol and maintained during the strictly necessary time to purchase those objectives. The nature and objectives of the research will be perfectly explained and clarified to the participants and they will have to sign an informed consent before their enrolment.

Each participant will be assigned with a code at the beginning of the study which does not allow to discover their identity. These codes will be current during the whole trial, thus patients will introduce it in questionnaires and daily surveys instead of any other personal data, such as name or surname. Therefore, data collected from participants will be saved in a password-protected file which will not contain any identifying information. During the data analyses phase, researchers will just have access to the participant code, without knowing the identity of the data which they are working it.

Nevertheless, we intend to make a daily surveillance of the patient progress, as well as to facilitate the contact with research responsible in case of any inconvenient emerges. For that reason, during the effective period of trial, from pre-treatment phase until post-treatment end, we will keep in touch with patients via telephone with a daily frequency. These conditions will be perfectly explained to the patients and the informed consent includes a clause to ensure that they give their authorization to be contacted by phone messages from researchers, limited to the clinical trial period. Only researchers who collaborate with the investigation will have access to the participants telephone number and these data will not be transferred to third parties under no circumstances. Telephone number will be just associated with the code given to the participant at the beginning of the trial.

Those participants who give their consent to, will be called and invited to the follow-up face-to-face assessment session six months after finishing their treatment to inquire as the long-term stability of accomplished clinical improvement. In any case, whether they decide to come or not, their phone number will be deleted and inaccessible once the investigation have finished.

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