Title: Predicting Pain Response to Transcranial Direct Current Stimulation for Phantom Limb Pain in Limb Amputees.

Protocol: 2015P002525

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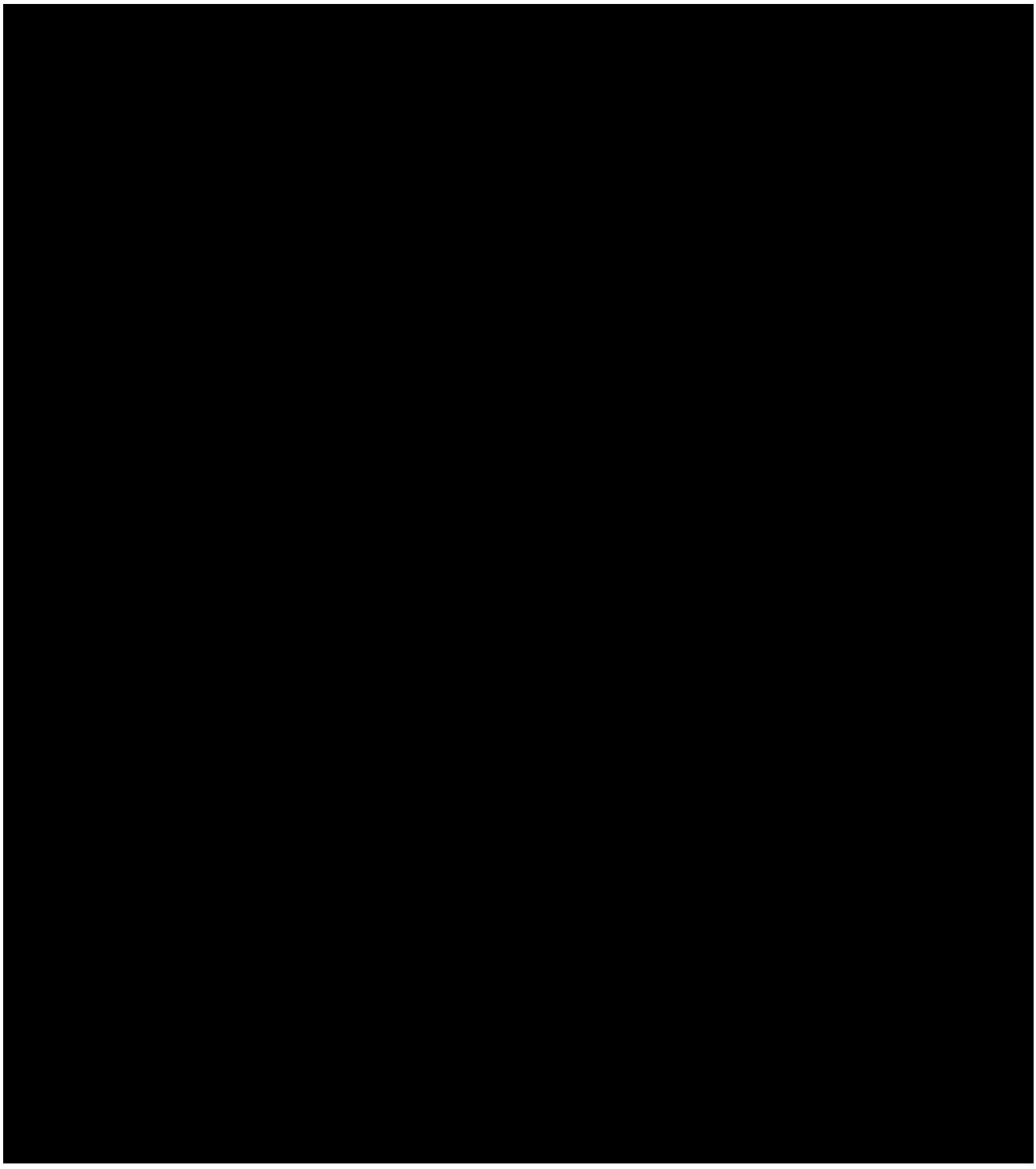
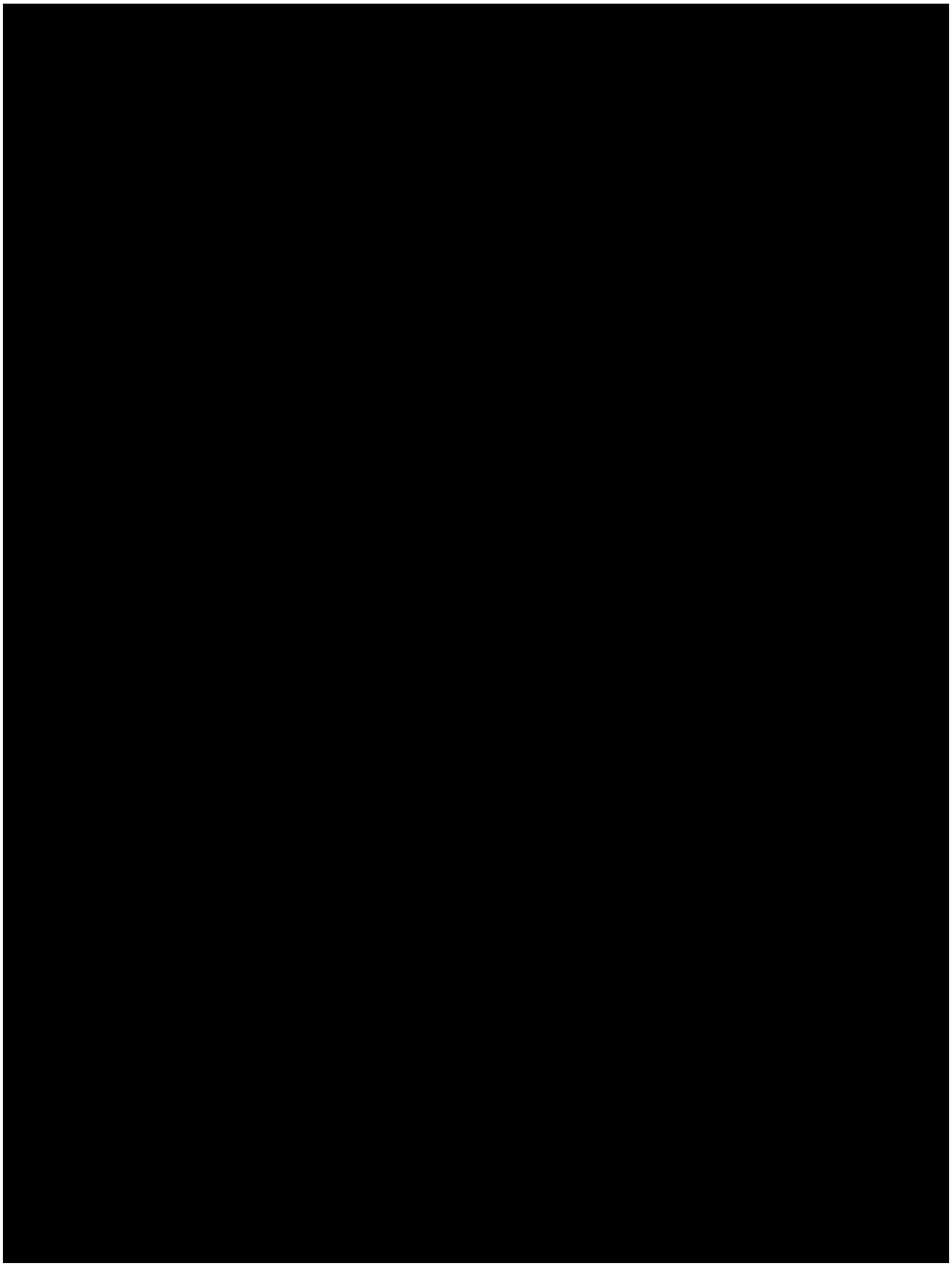




II. SPECIFIC AIMS

The specific aims of this experiment are as follows:

Aim 1: To assess the predictors of response to transcranial direct current stimulation (tDCS) in phantom limb pain of subjects with limb amputation. We will explore the aim 1 in an open-label pilot study in which patients will receive active tDCS during 5 daily sessions.

The primary endpoint will evaluate the predictors of pain response to tDCS measured by changes in PLP as indexed by a Visual Analog Scale. The study will require a total of 4 weeks to be completed. The first week, each patient will give daily reports of their pain using a VAS,

accounting for their PLP experience in the past 24hs. This initial baseline week will be followed by five days of treatment and a final 2-week follow-up period without any treatment to examine the lasting effects of the therapy. We will examine whether the following predictors are associated with treatment response: lower or upper limb, bilateral or unilateral and traumatic or non-traumatic amputation, baseline pain, age and gender by building a multivariate model.

IV. SUBJECT SELECTION

In this pilot study, we will recruit 50 subjects with phantom limb pain (PLP) of any etiology (traumatic, vascular disease, diabetic amputees or others). Subjects will need to meet all of the following inclusion criteria and none of the following exclusion criteria:

Inclusion Criteria:

1. Able to provide informed consent to participate in the study.
2. Subject is older than 18 years.
3. 3 months of phantom limb pain (experienced regularly for at least once a week) after the amputated limb has completely healed.*
4. Average pain of at least 4 on a numeric rating scale in the previous week (NRS; ranging from 0 to 10).
5. If the subject is taking any medications, dosages must be stable for at least 2 weeks prior to the enrollment of the study.

*The healing status of the limb will need to be confirmed by the subject's physician or by the physician of the protocol Dr. David Crandell (Co-Investigator).

Exclusion Criteria:

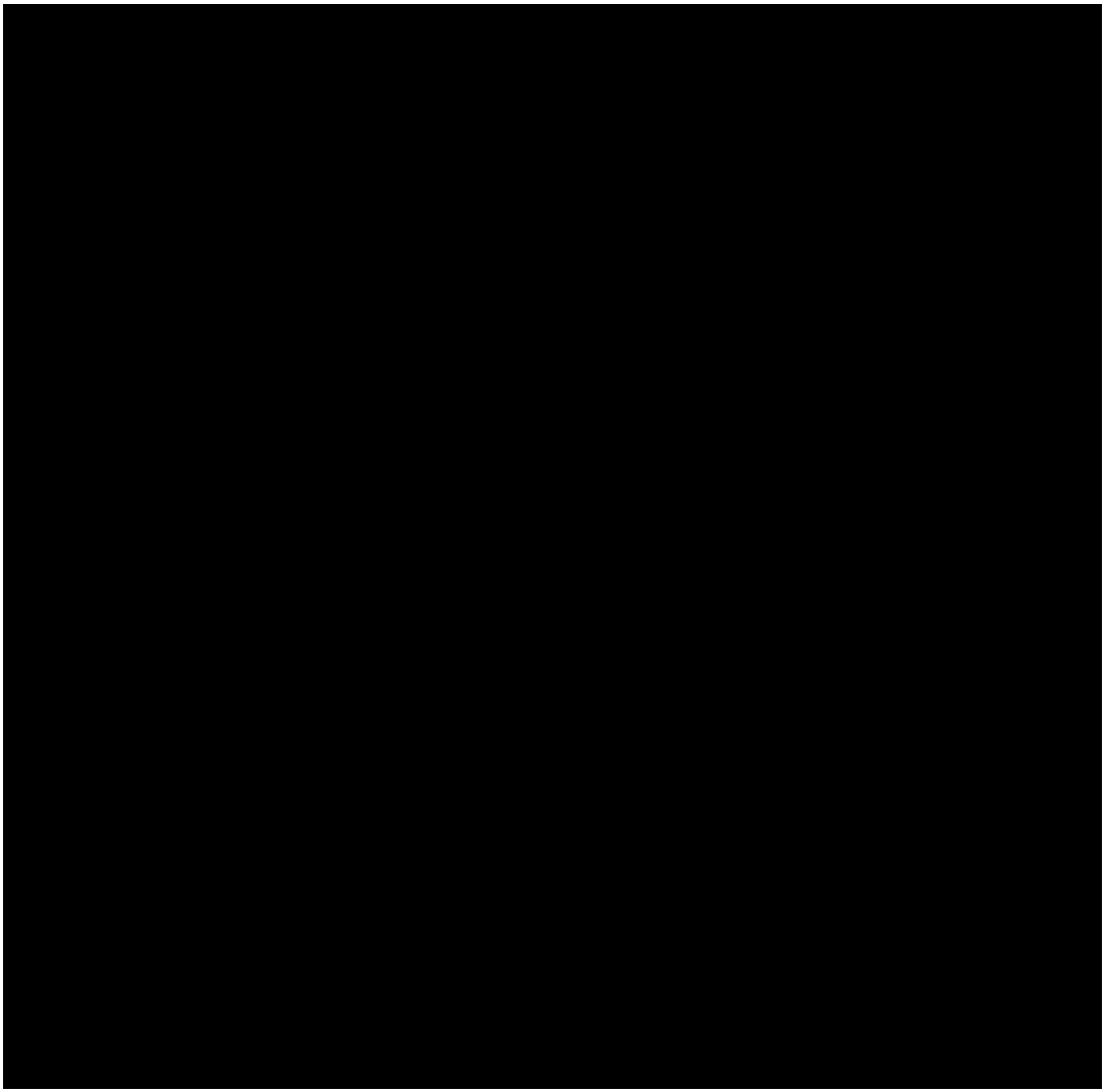
1. Pregnancy or trying to become pregnant in the next 2 months.
2. History of alcohol or drug abuse within the past 6 months as self-reported.
3. Presence of the following contraindication to transcranial direct current stimulation

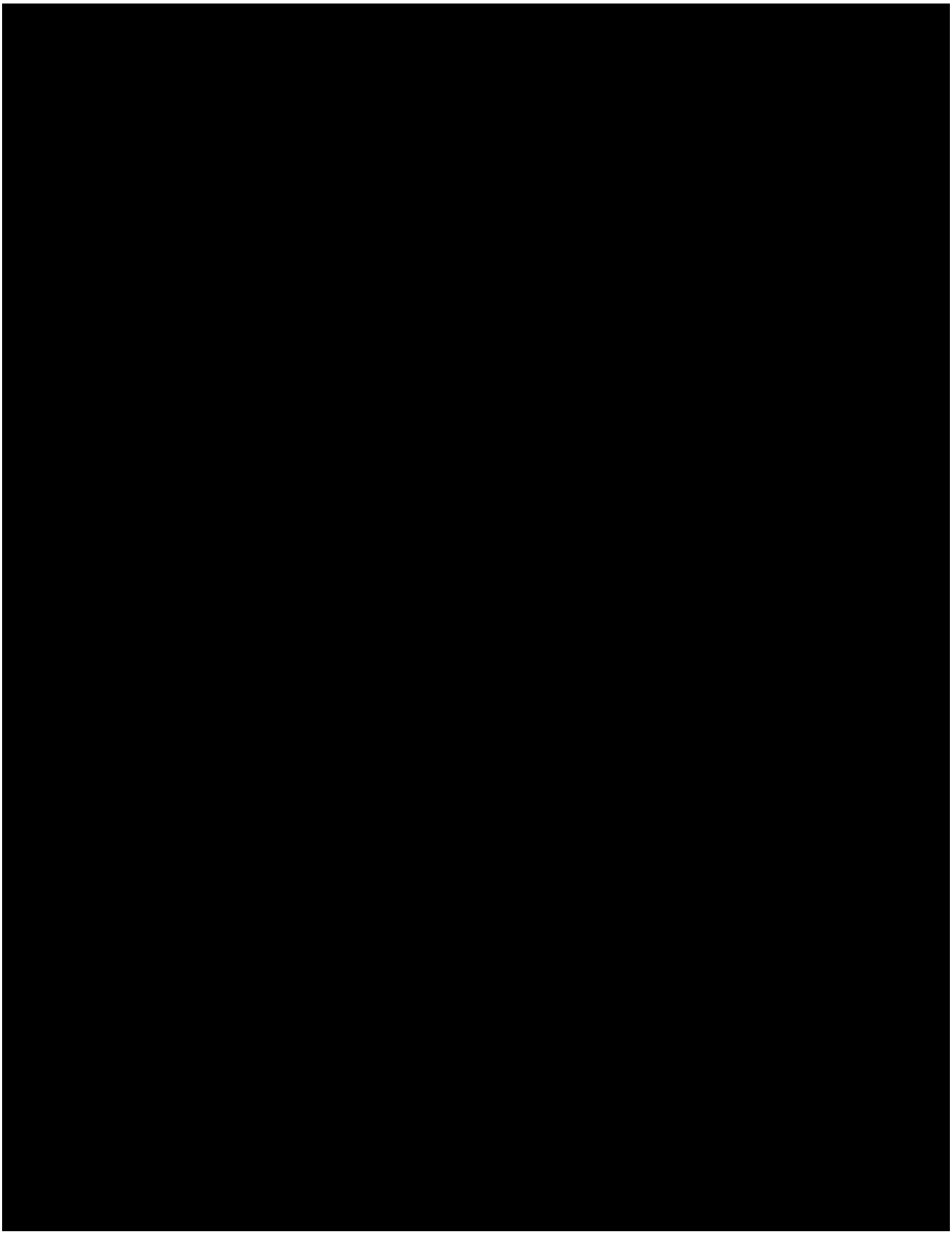
✓ Ferromagnetic metal in the head (e.g., plates or pins, bullets, shrapnel)

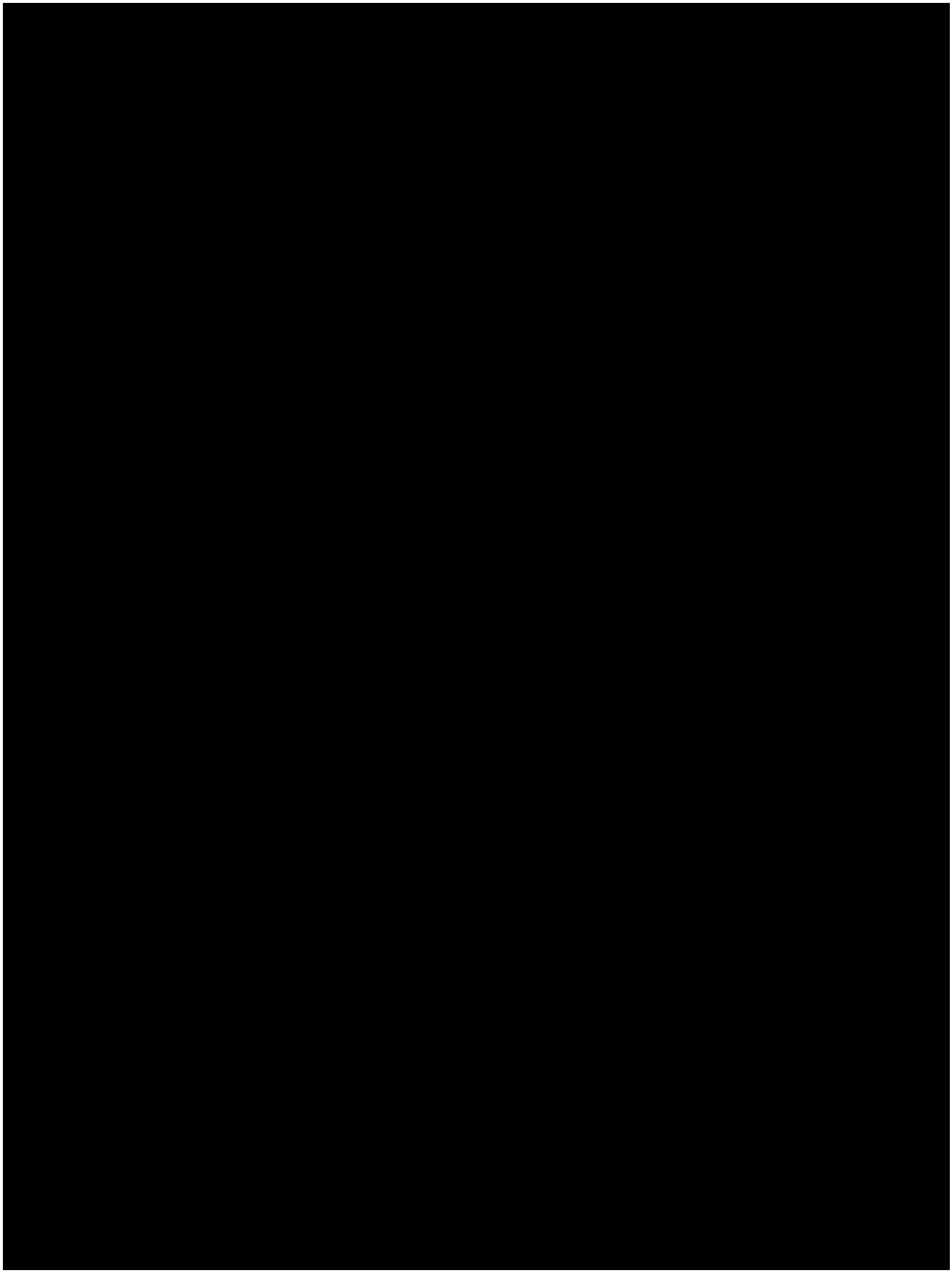
✓ Implanted head electronic medical devices (e.g., cochlear implants)

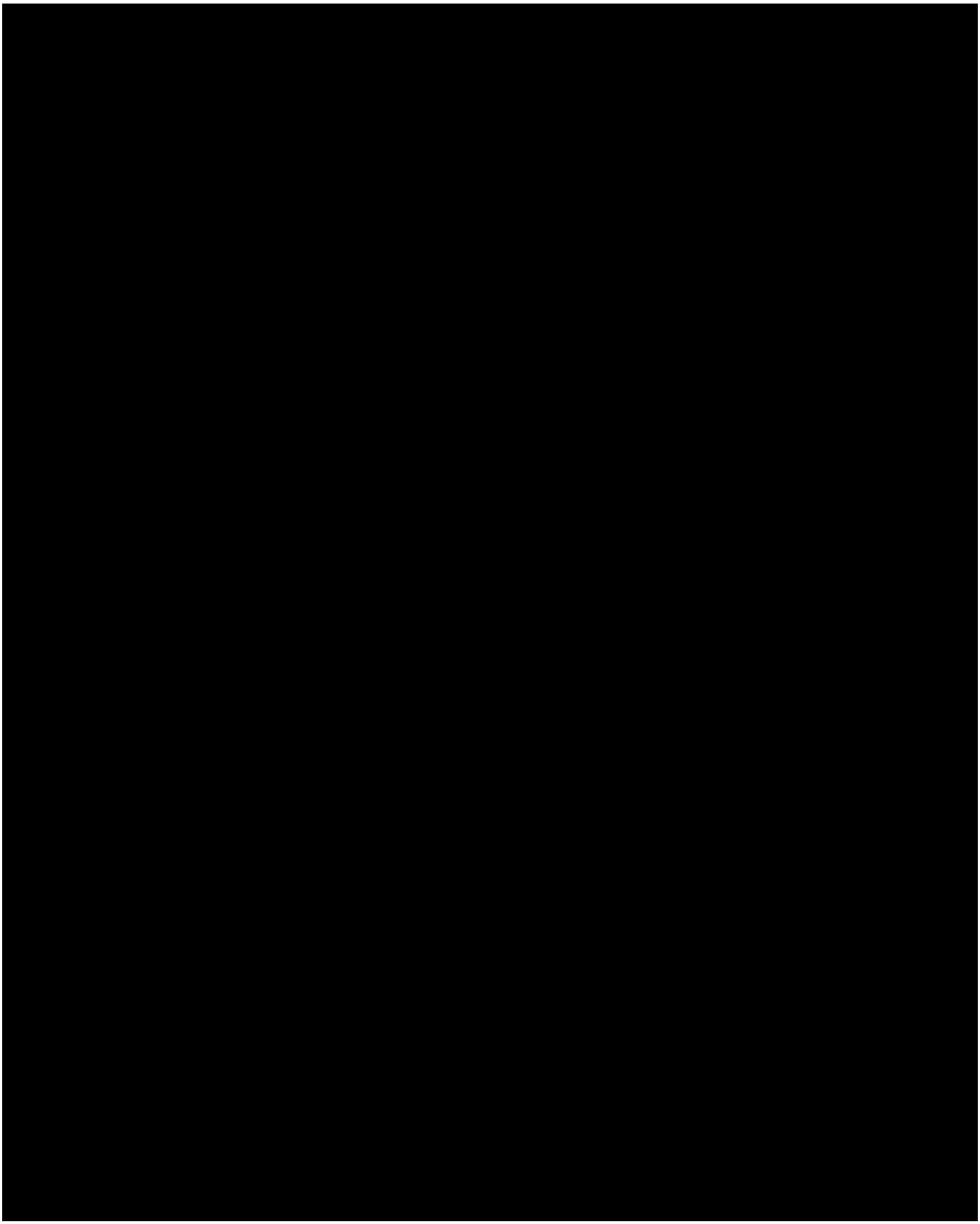
4. Head injury resulting in loss of consciousness for at least 30 min or pos-traumatic amnesia for greater than 24 hours, as self-reported

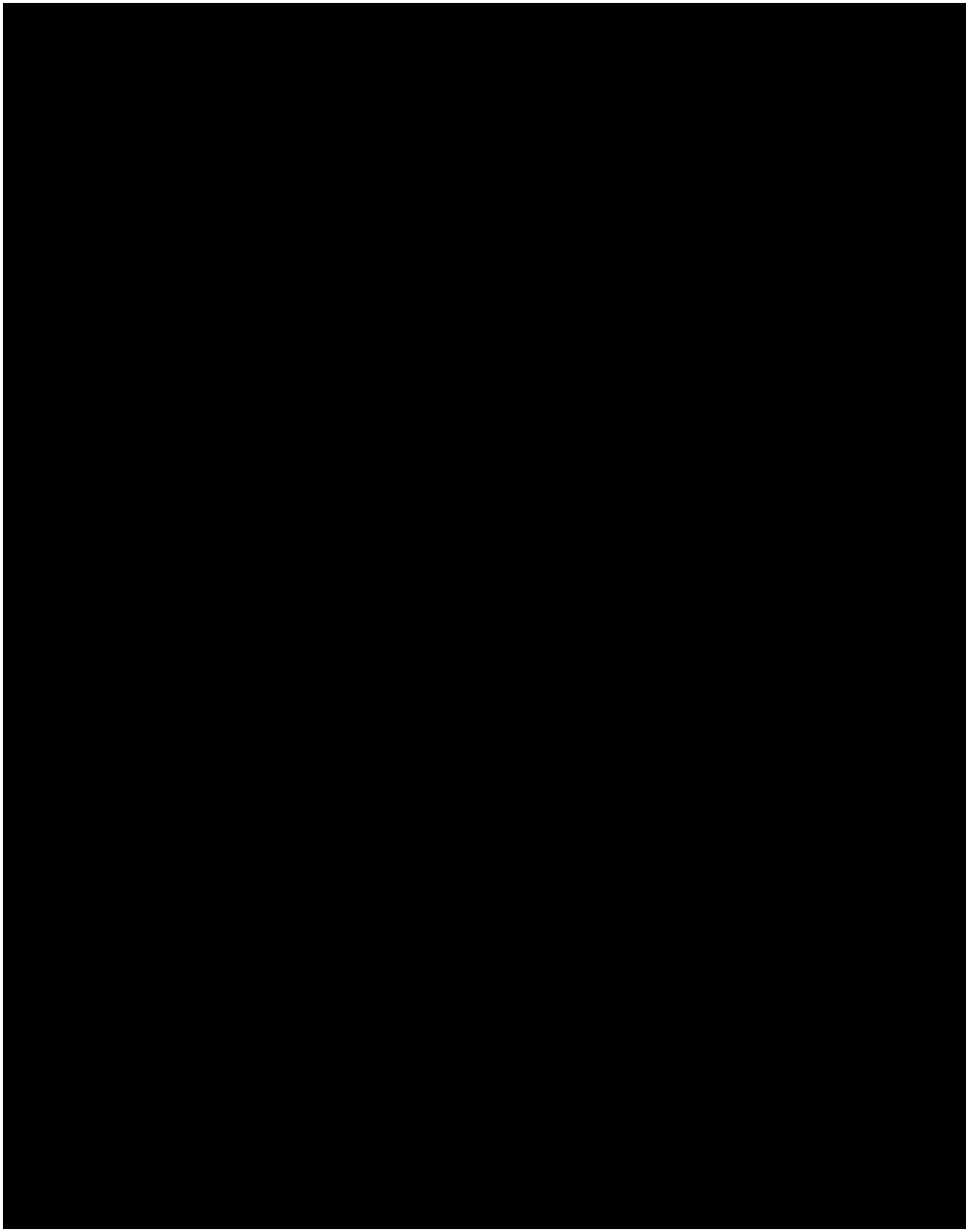
5. Unstable medical conditions (e.g. uncontrolled diabetes, uncompensated cardiac issues, heart failure or chronic obstructive pulmonary disease).
6. Uncontrolled epilepsy, as defined by previous clinical seizure in the past 3 months in patients with treatment for epilepsy.
7. Suffering from severe depression (as defined by a score of >30 in the Beck Depression Inventory).*
8. History of unexplained fainting spells or loss of consciousness as self-reported during the last 2 years.
9. History of neurosurgery, as self-reported.

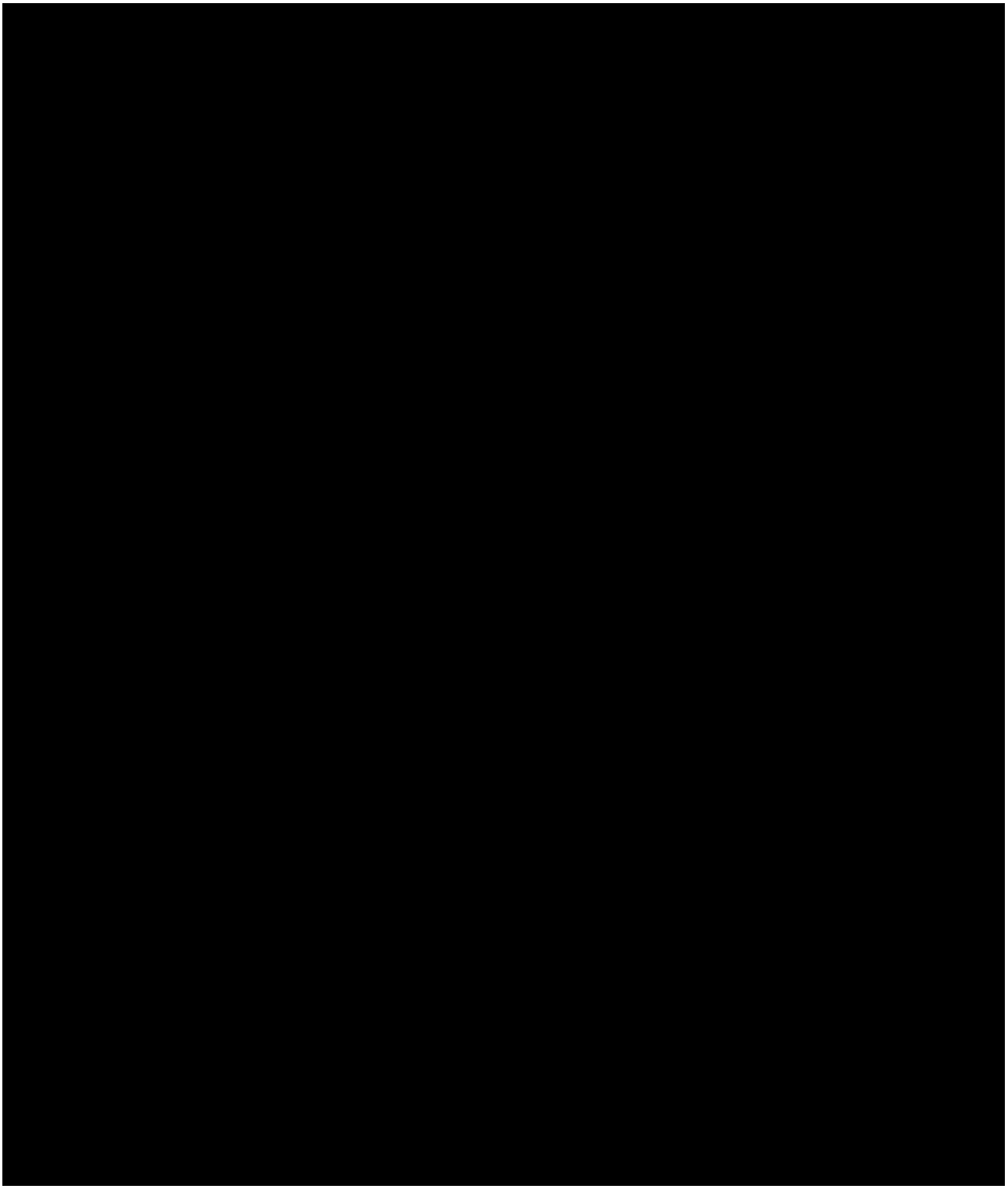












Description of interventions

tDCS Stimulation Protocol:

We will use Soterix Medical 1×1 tDCS stimulators device (© Soterix Medical Inc.), its sends a low-level current from the positive electrode, anode, to the negative electrode, cathode. During tDCS, low amplitude direct currents are applied via scalp electrodes and penetrate the skull to enter the brain. Direct current will be transferred by a saline-soaked pair of surface sponge electrodes (35 cm2) and delivered by a specially developed, battery-driven, constant current

stimulator with a maximum output of 10 mA. Subjects will receive daily stimulation sessions with active anodal tDCS for 5 days. Subjects are allowed to reschedule up to 1 stimulation visit. During each session, an anodal electrode will be placed over the primary motor cortex (M1), contralateral to the most painful amputation side and the cathode over the contralateral supraorbital area. Two milliamps of tDCS will be applied for 20 minutes [14].

DESCRIPTION OF ASSESSMENTS:

The following tests will be administered:

Visual Analogue Scale (VAS) for Pain: The VAS is a common assessment used which asks subjects to self-reportedly measure their pain on a visual scale (i.e., unbearable to none). We will use a VAS to determine subjects' pain scores. Subjects will rate their pain from 0 – indicating no pain at all, to 10 – indicating the worst pain felt. This scale is also colored, from green (at 0) to red (at 10), as a visual indicator of pain. This assessment tool is frequently used in many research studies evaluating pain levels [15, 19, 20].

Visual Analogue Scale (VAS) for Stump Pain: any painful sensation in the stump. Subjects will rate their stump pain from 0 – indicating no pain at all, to 10 – indicating the worst pain felt. The scale will include colors to help in identifying the correct response [15].

Visual Analog Scale (VAS) for Phantom Limb Sensation: all non-painful sensations in the amputated part of the limb. Subjects will be presented with a scale starting at 0- No phantom limb sensation, to 10 – Full sensation of the amputated limb. The scale will include colors to help in identifying the correct response [15].

Visual Analog Scale (VAS) for Phantom Limb telescoping: refers to the shrinking and retraction of the phantom towards the residual limb. Subjects will be presented with a scale starting at 0 - indicated that the phantom was enlarged, and 10 meant that the phantom was completely retracted into the stump the scale will include colors to help in identifying the correct response [15].

Adapted Groningen Questionnaire after Arm Amputation: This questionnaire will be applied to obtain information's concerning complaints that may be developed after arm amputation and has been used in several clinical trials assessing PLP [21].

Adapted Groningen Questionnaire after Leg Amputation: This questionnaire is originally meant to obtain information's concerning complaints that may be developed after arm amputation. We adapted the current arm version for lower limb amputation. This questionnaire [21] has been used in several clinical trials assessing PLP.

Pain and medication diary: To help monitor pain levels and medication use information, as well as safety. Subjects will be asked to record the number of phantom limb episodes on a daily basis, using a pain diary. They will record the intensity of the strongest episode as well as phantom limb sensation and stump pain on a colored visual analog scale included in the diary, where 0 represents no pain at all and 10 represents the highest pain the patient has ever felt. Moreover subjects will record their current medications and dosages daily in a pain medication diary, until completion of the study.

Beck depression Inventory: This self-report inventory consists of 21 multiple-choice questions and is widely used method to classify depression severity. It assesses for the presence of several symptoms related to depression, such as irritability, hopelessness and decreased cognitive performance. Physical symptoms such as weight loss and fatigue are also included. This instrument has been used previously to evaluate depression severity in patients with phantom limb pain [22], as well as in other chronic pain conditions [23, 24].

Beck anxiety Inventory: This self-report inventory consists of 21 multiple-choice questions about how the subject has been feeling in the last week, expressed as common symptoms of anxiety (such as numbness and tingling, sweating not due to heat, and fear of the worst happening). It is designed for an age range of 17–80 years old. Each question has the same set of four possible answer choices, which are arranged in columns and are answered by marking the appropriate one with a cross [25].

Mini Mental State examination (MMSE): This is a sensitive, valid and reliable 30-point questionnaire that is used extensively in clinical and research settings to measure cognitive impairment. This instrument will be used as a brief screening of cognitive abilities. It will be used as a baseline evaluation [26].

Quality of Life Assessment (Short version of SF-36): The short version of the SF-36 health survey is used as a measurement of quality of life. It provides a profile of functional health and well-being scores. It is also used as a psychometrical index of physical and mental health. This instrument is widely used as a quality of life assessment in patients after an amputation and those suffering from phantom limb pain [27-30].

Stroop test: In this task the subject is presented with names of colors written in the same color or in a different color, thus on the one hand the word names a color (red) and is written in another color (blue). In this task, the automatized behavior (reading) is in conflict with the desired response (naming the color). The Subject has to inhibit/suppress the automatic response of reading and naming the color the word is written in. The Stroop is one of the most commonly used tools for determining attentional problems, also used to assess executive function and working memory [31, 32]. Stroop test will be applied as a preliminary safety assessment of cognitive changes from baseline to post and follow-up visits.

Side Effects Questionnaire for tDCS: At each stimulation session, subjects will complete a questionnaire to evaluate potential adverse effects of tDCS (tingling, burning sensation, headache, neck pain, mood alterations) on a 4-point scale (None, mild, moderate and severe). The subjects will be asked whether they have experienced any side effects in an open-ended manner and they will then be specifically asked about headache, neck pain, scalp pain, scalp burns, tingling, skin redness, sleepiness, trouble concentrating, and acute mood change. If any side effects are reported, the degree of relatedness to the intervention will be assessed on a 5-point scale. This type of adverse events questionnaire has been used frequently in our previous tDCS studies [23], including in patients with phantom limb pain [33].

VI. BIOSTATISTICAL ANALYSIS

Data forms and questionnaires will be coded in a standardized manner, and double-entered into our database. Digital measures/recordings will be similarly tracked in our database and regularly backed up. Analyses will be conducted using standard statistical software such as SAS and Matlab.

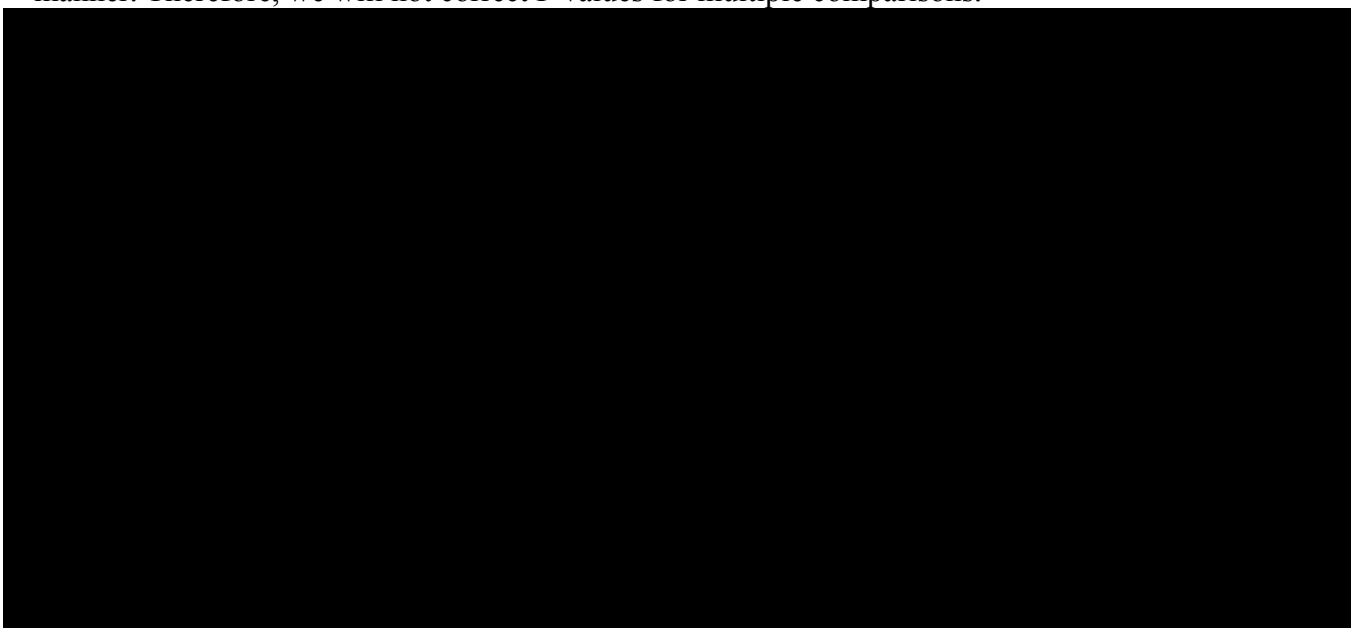
Sample size calculation:

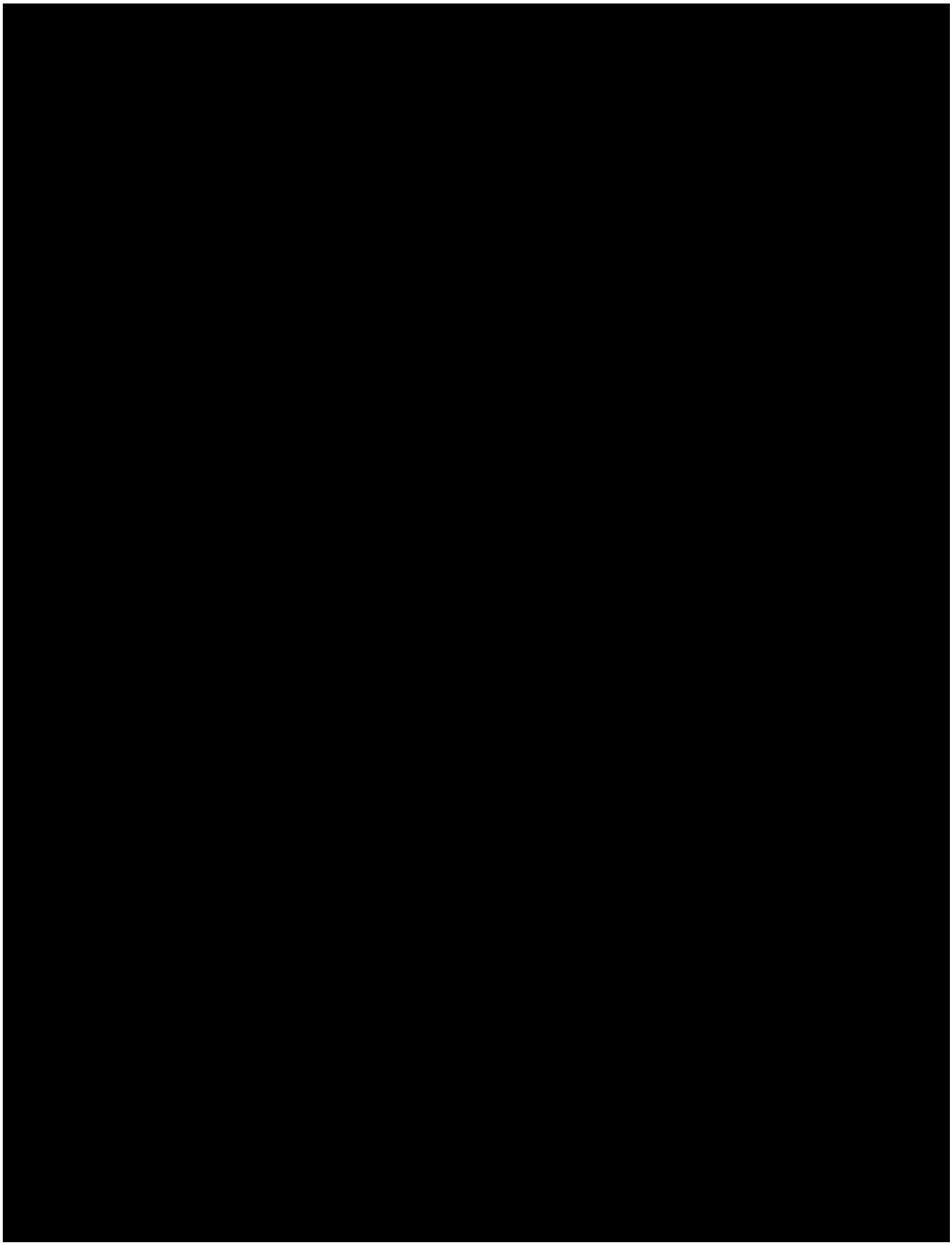
This is an open label pilot study, we aim to recruit 50 participants with upper or lower, bilateral or unilateral amputation of any etiology that present chronic phantom limb pain at least in one of the amputated limbs. Given we are planning to build a multivariate regression analysis with up to 5 variables and considering 10 subjects per variable, a sample of 50 subjects would be appropriate for this exploratory analysis. The goal of this study is to provide data to generate further hypothesis regarding whether demographic and clinical factors influence treatment response as to be used for designing a randomized clinical trial (RCT). Therefore the goal of this study is not confirm a priori hypothesis but to provide critical data to design a RCT testing the effects of tDCS in this population of PLP.

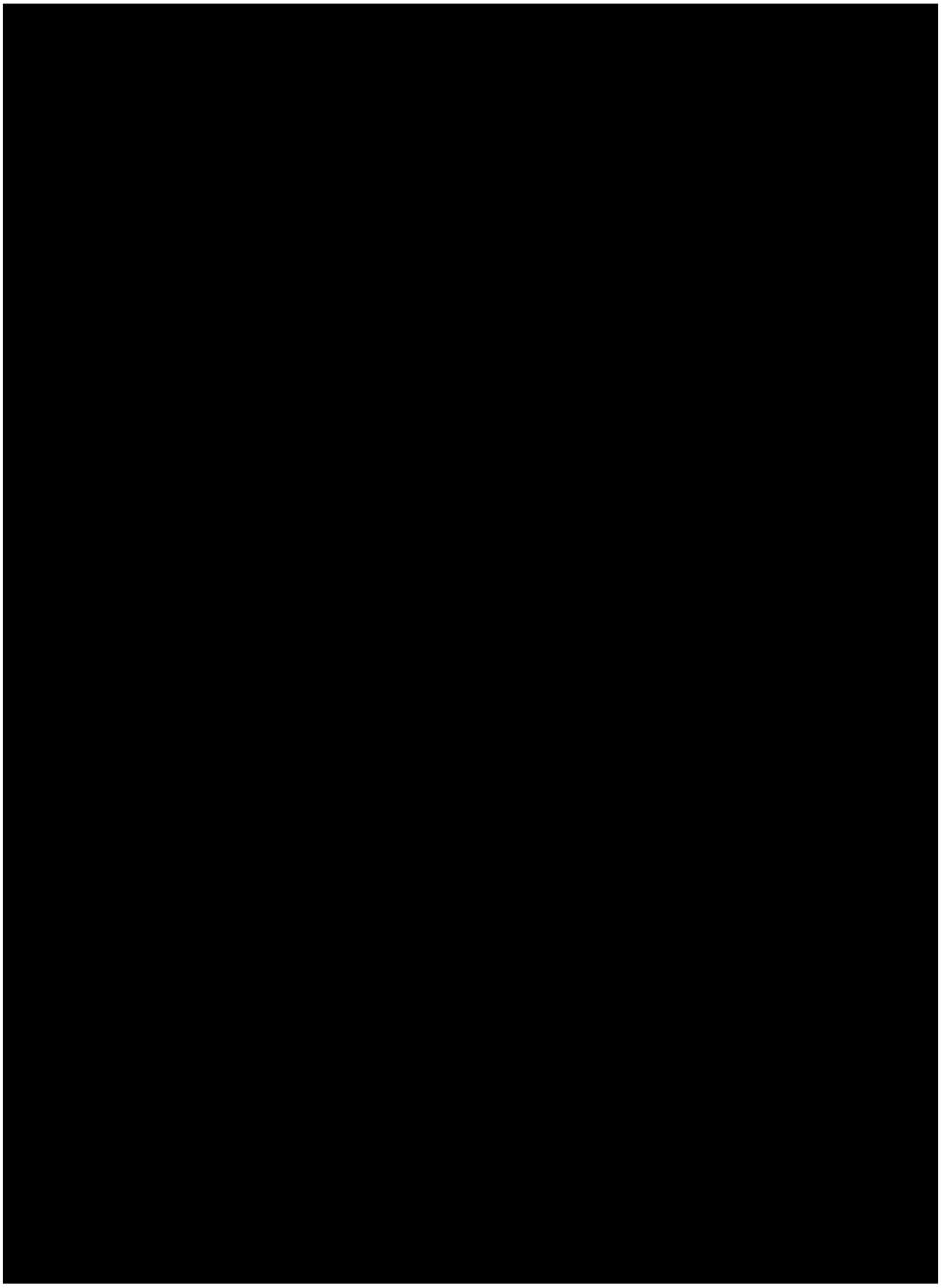
Statistical Analysis

*For aim 1:*The primary outcome is PLP indexed by VAS. PLP will be analyzed using changes in pain. To analyze these data, we will build a multivariate linear regression model in which the dependent variable will be the Visual Analogue Scale (VAS) for PLP using the following covariates: baseline pain (VAS), amputated limb (upper/lower), etiology of amputation (traumatic/ non traumatic), laterality of amputation (unilateral/bilateral), age, and gender. The first step will be perform a univariate analysis for each one of our predictors using univariate linear regression and obtain the values for the unadjusted b coefficients and 95% confidence intervals (CIs). After that, predictors associated with the outcome at a p level <0.01 will be used to build a multivariate linear regression using a forward stepwise model.

Additional statistical models for secondary outcomes will be developed in an exploratory manner. Therefore, we will not correct P values for multiple comparisons.







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