

# Schizophrenia Treatment with electric Transcranial Stimulation (STARTS): design, rationale and objectives of a randomized, double-blinded, sham-controlled trial

Tratamento da esquizofrenia com estimulação transcraniana por corrente contínua (ETCC): fundamentação teórica e objetivos de um ensaio clínico randomizado, duplo-cego, controlado por simulação

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## Abstract

**Introduction:** Schizophrenia is a severe mental disorder. While some antipsychotic medications have demonstrated efficacy in treating positive symptoms, there is no widely recognized treatment for negative symptoms, which can cause significant distress and impairment for patients with schizophrenia. Here we describe the rationale and design of the STARTS study (Schizophrenia Treatment with electric Transcranial Stimulation), a clinical trial aimed to test the efficacy of a non-pharmacological treatment known as transcranial direct current stimulation (tDCS) for treating the negative symptoms of schizophrenia.

**Methods:** The STARTS study is designed as a randomized, sham-controlled, double-blinded trial evaluating tDCS for the treatment of the negative symptoms of schizophrenia. One-hundred patients will be enrolled and submitted to 10 tDCS sessions over the left dorsolateral prefrontal cortex (anodal stimulation) and left temporoparietal junction (cathodal stimulation) over 5 consecutive days. Participants will be assessed using clinical and neuropsychological tests before and after the intervention. The primary outcome is change in the Positive and Negative Syndrome Scale (PANSS) negative subscale score over time and across groups. Biological markers, including blood neurotrophins and interleukins, genetic polymorphisms, and motor cortical excitability, will also be assessed.

**Results:** The clinical results will provide insights about tDCS as a treatment for the negative symptoms of schizophrenia, and the biomarker investigation will contribute towards an improved understanding of the tDCS mechanisms of action.

**Conclusion:** Our results could introduce a novel therapeutic technique for the negative symptoms of schizophrenia.

**Clinical trial registration:** ClinicalTrials.gov, NCT02535676.

**Keywords:** Schizophrenia, electric stimulation therapy, randomized controlled trial, biological markers, transcranial stimulation.

## Resumo

**Introdução:** A esquizofrenia é um transtorno mental grave. Embora alguns medicamentos antipsicóticos tenham demonstrado eficácia no tratamento de sintomas positivos, não há tratamento amplamente reconhecido para sintomas negativos, o que pode causar sofrimento e prejuízo significativos para pacientes com esquizofrenia. Aqui descrevemos a fundamentação teórica e o design do estudo STARTS (Schizophrenia Treatment with electric Transcranial Stimulation), um ensaio clínico destinado a testar a eficácia de um tratamento não farmacológico conhecido como estimulação transcraniana por corrente contínua (ETCC) para tratar os sintomas negativos da esquizofrenia.

**Métodos:** O estudo STARTS foi concebido como um ensaio clínico randomizado, controlado por simulação, duplo-cego, avaliando a ETCC para o tratamento dos sintomas negativos da esquizofrenia. Cem pacientes serão incluídos e submetidos a 10 sessões de ETCC sobre o córtex pré-frontal dorsolateral esquerdo (estimulação anódica) e a junção temporoparietal esquerda (estimulação catodal) durante 5 dias consecutivos. Os participantes serão avaliados através de testes clínicos e neuropsicológicos antes e após a intervenção. O desfecho primário é a mudança na pontuação da subescala negativa da Escala da Síndrome Positiva e Negativa (Positive and Negative Syndrome Scale [PANSS]) ao longo do tempo e entre os grupos. Marcadores biológicos, incluindo neurotrofinas e interleucinas do sangue, polimorfismos genéticos e excitabilidade cortical motora, também serão avaliados.

**Resultados:** Os resultados clínicos fornecerão informações sobre a ETCC como um tratamento para os sintomas negativos da esquizofrenia, e a investigação dos biomarcadores contribuirá para uma melhor compreensão dos mecanismos de ação da ETCC.

**Conclusão:** Nossos resultados podem trazer uma nova técnica terapêutica para o tratamento dos sintomas negativos da esquizofrenia.

**Registro do ensaio clínico:** ClinicalTrials.gov, NCT02535676.

**Descritores:** Esquizofrenia, terapia de estimulação elétrica, ensaio clínico randomizado, marcadores biológicos, estimulação transcraniana.

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## Introduction

Schizophrenia is a severe mental illness that significantly impacts well-being. The negative symptoms of the disorder include blunted affect, apathy, avolition, and anhedonia, and are responsible for a large proportion of the disease burden. These symptoms represent an important clinical challenge,<sup>1,2</sup> and several studies have associated negative symptoms with lower premorbid functionality, lower IQ, and poorer clinical outcome.<sup>3-7</sup> Negative symptoms have a clinical course independent from positive symptoms, are stable or increasing in severity over time, and have an independent prognostic weight.<sup>3-7</sup> Although antipsychotic medications are an effective treatment for positive symptoms and are always recommended for schizophrenia, negative symptoms tend to persist or even worsen in the presence of antipsychotic medication treatment, and no effective treatment for negative symptoms has shown strong supportive evidence.<sup>8</sup>

Evidence for the pathophysiology of negative symptoms points to the involvement of the dorsolateral prefrontal cortex (DLPFC), as neuroimaging studies have shown reduced metabolism in the prefrontal cortex in patients with schizophrenia both with and without medication,<sup>9,10</sup> along with an inverse correlation between negative symptom severity and cerebral blood flow in the prefrontal cortex.<sup>11</sup> Hypoactivation of prefrontal regions also seems to be related to the presence of negative symptoms in schizophrenia.<sup>12</sup> These findings suggest that these areas could be a target for focal interventions by non-invasive brain stimulation, as such stimulation may improve the physiological deficits of the disorder and exert therapeutic effects. Repetitive transcranial magnetic stimulation (rTMS) uses alternating magnetic fields to induce an electric current in cortical tissue<sup>13</sup> and can change dopamine concentration in prefrontal regions.<sup>14</sup>

rTMS protocols have been investigated as possible treatments for schizophrenia<sup>15-26</sup>; most protocols for negative symptoms have used high frequency stimulation and targeted the DLPFC. However, meta-analyses evaluating the efficacy of rTMS using this approach have shown discordant results.<sup>27,28</sup> rTMS has also been used to treat auditory hallucinations in schizophrenia, a symptom typically associated with hyperactivity of the left temporoparietal cortex. rTMS protocols designed to inhibit cortical activity in this region have proven generally effective to treat auditory hallucinations.<sup>28</sup>

Transcranial direct current stimulation (tDCS) is another form of non-invasive brain stimulation under research for the treatment of various neuropsychiatric

conditions, with encouraging results.<sup>29-31</sup> This mode of non-invasive brain stimulation has several advantages and could potentially be included as a treatment option for schizophrenia.<sup>32</sup> tDCS consists of the placement of two electrodes (a cathode and an anode) over the scalp to deliver an electric current of small and constant intensity. The electric current that flows through the cerebral cortex during the tDCS session modifies the electric potential of the extracellular space. As a result, cortical regions close to the anode present a decrease in transmembrane electric potential and an associated increase in neuronal firing rate, while the regions close to the cathode present an increase in transmembrane electric potential and a decrease in neuronal firing rate.<sup>33-35</sup>

tDCS offers some advantages relative to TMS, including 1) portability: tDCS devices are small and portable, allowing for treatment in many different settings, including home treatment, which is especially attractive for patients with limited mobility; 2) duration: the effects of tDCS have longer duration; 3) cost: while the price of an average TMS device varies between 20 and 100,000 U.S. dollars, the cost of a tDCS device ranges between 400 and 10,000 U.S. dollars.<sup>36</sup>

For these reasons, tDCS may represent a promising tool for the treatment of schizophrenia. According to current models of cortical pathophysiology in schizophrenia and the mechanisms of action of tDCS, anodal stimulation of the left DLPFC would generate an increase in activity in this area, leading to an improvement of negative symptoms, while cathodal stimulation of the temporoparietal cortex would decrease cortical activity at the same time, leading to an improvement in hallucinations. This simultaneous excitatory and inhibitory stimulation is possible with tDCS because both the anode and cathode must be placed on the scalp to close the circuit and allow the electric current to pass. A previous study designed to treat auditory hallucinations using this method reported a significant decrease in negative symptoms.<sup>37</sup> The main aim in this clinical trial is to confirm this hypothesis in a study designed specifically for the treatment of negative symptoms.

The primary objective of this study is to evaluate the efficacy of active tDCS for the treatment of the negative symptoms of schizophrenia, as measured by reduction of the Positive and Negative Syndrome Scale (PANSS) negative symptoms subscale scores 6 weeks after beginning the treatment, relative to sham tDCS.

The secondary objectives are to evaluate:

- 1) the efficacy of tDCS for the treatment of auditory hallucinations, as measured by the Auditory Hallucination Rating Scale (AHRS);

- 2) response rate, defined as a reduction of  $\geq 20\%$  in PANSS negative symptoms subscale scores;
- 3) efficacy in treating positive symptoms, as measured by the PANSS positive symptoms subscale;
- 4) efficacy in treating depressive symptoms associated with schizophrenia, as measured by the Calgary Depression Scale for Schizophrenia;
- 5) change in overall functioning, as measured by the Global Assessment of Functioning (GAF);
- 6) changes in several blood biomarkers;
- 7) changes in cognitive measurement.

## Methods

### Design and study population

STARTS is a randomized, double-blinded, placebo-controlled trial. Eligible patients will be recruited from Instituto de Psiquiatria, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo (USP), São Paulo, SP, Brazil, Instituto Bairral de Psiquiatria, Itapira, SP, Brazil, and the primary care services in the respective catchment areas. The study began in September 2014 and plans to enroll 100 participants. Participants who meet the inclusion criteria and agree to participate in the study will be allocated (1:1) into one of two groups, defined as sham or active tDCS. Subjects will receive 10 tDCS sessions over 5 consecutive days. Baseline measurements will be performed before the first session, and follow-up measurements related to the primary outcome will be measured 6 weeks after the first session. Volunteers who do not show an improvement in negative symptoms (defined as a reduction of  $\geq 20\%$  in the negative PANSS score or maintenance of a total negative PANSS score  $\geq 20$  points) after having been allocated to the sham group may elect to receive 5 days of active stimulation twice daily (partial cross-over).

### Inclusion and exclusion criteria

This clinical trial was designed to include males and females diagnosed with schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), aged between 18 and 65 years. Potential participants will be screened by a trained psychiatrist to ensure fulfillment of all inclusion criteria. In addition to the PANSS, the Structured Clinical Interview for DSM-IV (SCID) will be applied during the screening interview to confirm the diagnosis of schizophrenia. Patients will only be included if they present a minimum score of 20 points in the sum of the negative symptoms' subscale, are under proper antipsychotic treatment, and

have stable positive symptoms. Other drugs that may interfere with the assessment of negative symptoms, including antidepressants, modafinil, erythropoietin, and minocycline will be washed-out for at least 4 weeks before trial onset. Medication type and dosage will be monitored during participation in the clinical trial, and changes in non-psychotropic medication or psychosocial interventions will be allowed.

Exclusion criteria are unstable medical illness, pretreatment with rTMS or tDCS, psychiatric comorbidities (such as mood disorders, personality disorders, abuse or dependence on alcohol or drugs, or use of any illicit drug during the last 6 months), current or previous electroconvulsive therapy during the last 6 months, use of benzodiazepines in doses equal to or higher than 10 mg of diazepam or the equivalent, and the presence of specific contraindications to tDCS such as electronic or metal implants in the cephalic segment. We will include any stage of the disease provided the patient is under stable psychotropic medication and dosage for at least 6 weeks.

Recruitment strategies include a convenience sample of patients with schizophrenia from outpatient and inpatient clinics referred and screened by psychiatrists specialized in psychotic disorders, and spontaneous enrollment through advertisements in local newspapers, radio stations, and websites.

### Measurement of variables and outcomes

Demographic and clinical profiles will be assessed with the following variables: gender, age, years of education, socioeconomic status, medical and psychiatric comorbidities, refractoriness to current psychotic symptoms, duration of current psychotic episode, number of previous hospitalizations for psychotic episodes, and previous treatment with electroconvulsive therapy. Besides, we will assess information regarding predictors of response or refractoriness, e.g.: type and dose of the current antipsychotic drug (in chlorpromazine equivalents), adherence to the current treatment, duration of untreated psychosis and age upon the first episode of schizophrenia.

The primary outcome will be measured with the PANSS negative symptoms subscale.<sup>38</sup> The PANSS will also be used categorically to separate subjects into responders ( $\geq 20\%$  reduction in scale) and non-responders ( $< 20\%$  improvement in scale).

Each participant will be evaluated at baseline, at day 5, week 2, week 4, week 6, and week 12 (Table 1). The PANSS, Auditory Verbal Hallucinations Scale (AVHS), and Calgary Depression Scale for Schizophrenia (CDSS) will be applied at all evaluations and at baseline. We will apply the Scale for Assessment of Negative

Symptoms (SANS), the Social and Occupational Functional Assessment Scale (SOFAS), and the Clinical Global Impression Scale (CGI), and the participant will complete the World Health Organization Quality of Life instrument-Abbreviated version (WHOQOL-Bref) at baseline and at week 6. We will use a tDCS questionnaire for adverse effects to assess treatment tolerability.<sup>39</sup> Blinding efficacy will be assessed at endpoint by asking raters and participants to guess their allocation group.

### Randomization and allocation

Randomization will be generated through the website [www.randomization.com](http://www.randomization.com) and will be performed in blocks to allow permutation of block size and order. Patient allocation will be carried out using sealed, opaque, patterned envelopes, labeled with a random number assigned to the participant. The envelope will be opened and the participant will receive either active or sham treatment according to the code contained in the envelope upon signature of the informed consent form and inclusion in the trial.

### Intervention

A tDCS session involves the placement of two electrodes over the scalp. The anode will be positioned over the area corresponding to the left DLPFC, between F3 and FP1, and the cathode will be positioned over the area of the left temporoparietal junction (CP5). The minimum distance between electrodes is 7 cm, the electrode dimensions are 5 × 7 cm, and the applied current will be 2 mA. We will use the DC Stimulator tDCS device (Neuroconn®, Ilmenau, Germany) in study mode for double-blind trials. Each session will last 20 minutes, and participants will receive two sessions a day over 5 consecutive days (Monday to Friday).

### Blinding

This is a double-blind study: researchers, tDCS technicians, and patients will have no knowledge of the treatment administered to each participant until the end

of the study. Technicians will not be allowed to assess the participants.

The tDCS technique is particularly advantageous for ensuring blinding when compared to other noninvasive brain stimulation techniques, as the session provokes only a mild tingling sensation which is habituated in seconds. Given this feature, sham stimulations were designed to deliver only a few seconds of electric current in the beginning of the session and then shut down and provide no electric current for the rest of the session, simulating an active session but providing no clinical or physiological effects.<sup>40,41</sup>

The tDCS device set on study mode requires the technician to enter one of 200 5-digit codes into the device before the session, corresponding to either an active session with parameters as described above, or a sham session. Each participant will be assigned a code according to the intervention group to which they were assigned, found in the randomization envelope. The correspondence between the participant's code and the intervention delivered will remain unknown to the team and the participants, preserving blinding.

### Sample size calculation

Sample size calculation is based on the PANSS negative symptom score, which is the primary outcome of our study. In previous studies, this score has shown an average variation from 20 to 24 points in this type of patient, and a difference of 3 points is considered clinically significant. Standard deviations in previous studies have shown values between 4-5 points.<sup>24,38,42</sup> Therefore, a study with 80% power and alpha of 0.05 requires a sample of 44 patients in each group. We expect a dropout rate of 15%, suggesting an enrollment of about 50 patients per group.

### Statistical analysis

Statistical analyses will be performed using Stata 12 SE programs and the Statistical Package for the Social Sciences (SPSS) version 17 for Windows. All analyses

**Table 1** - Measurement outcomes over time

	Baseline	Week 1	Week 2	Week 4	Week 6	Week 12
PANSS	X	X	X	X	X	X
SANS	X				X	
CDSS	X	X	X	X	X	X
Cognitive test	X				X	
Blood sample	X				X	
Motor excitability	X				X	X

CDSS = Calgary Depression Scale for Schizophrenia; PANSS = Positive and Negative Syndrome Scale; SANS = Scale for Assessment of Negative Symptoms.

will be performed according to the intention to treat principle (all patients will be included in the analysis).

We will use a general linear model with a continuous dependent variable (PANSS negative symptom score) for the primary outcome measure. Secondary analyses will use the same model, and scores obtained on the other scales will be used as dependent variables. The analyses are considered significant at  $p < 0.05$ .

Exploratory analyses will include other variables potentially influencing the therapeutic effect, including education, number of previous hospitalizations, presence of medical comorbidities, and other socioeconomic variables. Refractoriness to antipsychotic medication will be analyzed as a dichotomous variable, defined as presence or absence of refractoriness.

### **Cognitive assessments**

The participants will be tested at baseline and at week 6 with the Penn Computerized Neurocognitive Battery (Penn-CNB). The Penn-CNB takes an average of 1 hour to perform and assesses the following domains<sup>43</sup>: executive control (attention, working memory and abstraction, and mental flexibility), episodic memory (verbal, facial, and spatial), complex cognition (spatial processing), social cognition (emotion discrimination, emotion recognition, and emotional accuracy) and sensory-motor processing (motor praxis and pressing the fingers test).

### **Biological markers**

Blood samples will be collected from all participants at baseline and at week 6, and the biomarkers described below will be analyzed. A portion of these samples will be frozen for posterior analysis.

- a) Brain-derived neurotrophic factor (BDNF): BDNF is a neurotrophin related to synaptic strengthening, neurodevelopment, and neuroprotection,<sup>44</sup> and has been associated with several psychiatric disorders. BDNF gene polymorphisms are associated with better cognitive performance in patients with schizophrenia.<sup>45</sup> Another useful approach for studying the role of this biomarker in schizophrenia is the measurement of plasma or serum BDNF levels, as this biomarker can cross the brain-blood barrier.<sup>44</sup> Blood BDNF levels appear to be lower in patients with chronic schizophrenia compared to controls,<sup>46,47</sup> and some studies examining BDNF levels before and after treatment found increased levels following the use of antipsychotics.<sup>48,49</sup> Plasma BDNF levels and BDNF gene polymorphisms will be analyzed with respect to tDCS treatment response.
- b) Motor cortical excitability: Studies using TMS-elicited motor evoked potentials have

shown alterations in the cortical excitability of patients with schizophrenia, suggesting a global dysfunction of GABAergic activity, in alignment with previous pathophysiological models of schizophrenia.<sup>50</sup> We will take a series of measurements of cortical excitability using TMS-elicited motor evoked potentials following the guidelines for the technique,<sup>51</sup> both at baseline and during the follow-up evaluation. Our goal is to analyze cortical excitability variables as possible predictors and markers of the clinical outcomes of tDCS treatment for schizophrenia.

- c) Other genetic biomarkers: several single nucleotide polymorphisms (SNPs) have been associated with schizophrenia, including GRIA1, ERBB4, DRD2, CACNA1C, and NRG1.<sup>52</sup> These SNPs may play a role in the treatment response to tDCS.

### **Expected results**

Our primary hypothesis is that participants receiving active tDCS will present a reduction of negative symptoms as measured by the PANSS, compared to patients receiving sham tDCS. The results of this study will additionally contribute to the development of further studies on neuromodulation for the treatment of schizophrenia.

### **Sources of funding**

We receive financial support from Instituto Nacional de Biomarcadores em Neuropsiquiatria (INBioN) for the analysis of biomarkers, and from the Stanley Medical Research Institute for performing the clinical trial.

### **Computer modelling of tDCS generated electric fields**

We have designed a computer model of the electric field generated by the tDCS montage proposed in this clinical trial. We simulated this electric field using the SimNIBS modelling environment,<sup>53</sup> which relies on a finite element model of brain current flow based on an magnetic resonance imaging (MRI)-derived template head model.<sup>54</sup>

Electrode disposition in this montage includes the placement of two electrodes with dimensions 5 x 7 cm over the participant's scalp, with the anode centered above F3 (10-10 EEG International System) and the cathode centered above CP5, delivering an electric current of 2 mA. A depiction of the montage is provided in Figure 1.

The model predicts a diffuse electric field spreading from the left frontal lobe to the left temporoparietal cortex, reaching maximum intensity in the cortical



area around the central sulcus. An image of the results yielded by the simulation is presented in Figure 2.

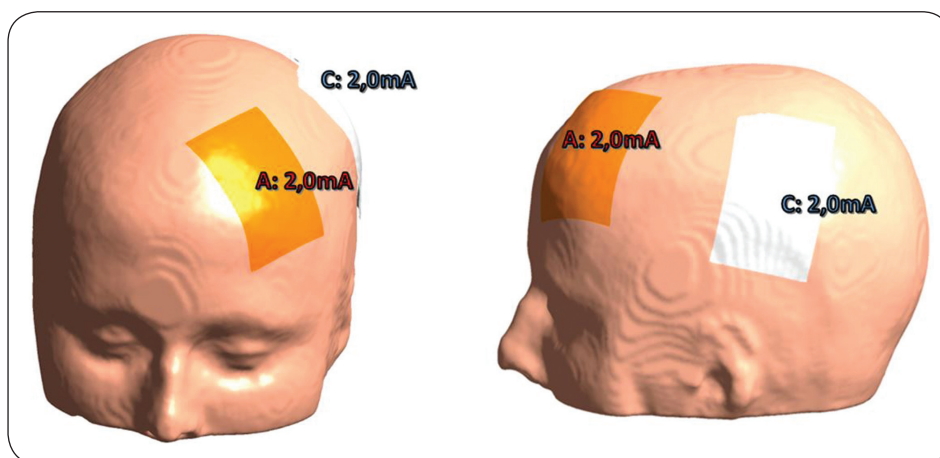
Similar results were found previously using the same montage, and despite the high intensity of the electric field in a region without clinical interest between the electrodes (primary motor cortex and primary somatosensory cortex), the predicted intensity of the electric field in the regions of interest (the DLPFC and temporoparietal junction) was considered satisfactory for possible clinical trials investigating the treatment of schizophrenia symptoms.<sup>53-55</sup>

## Discussion

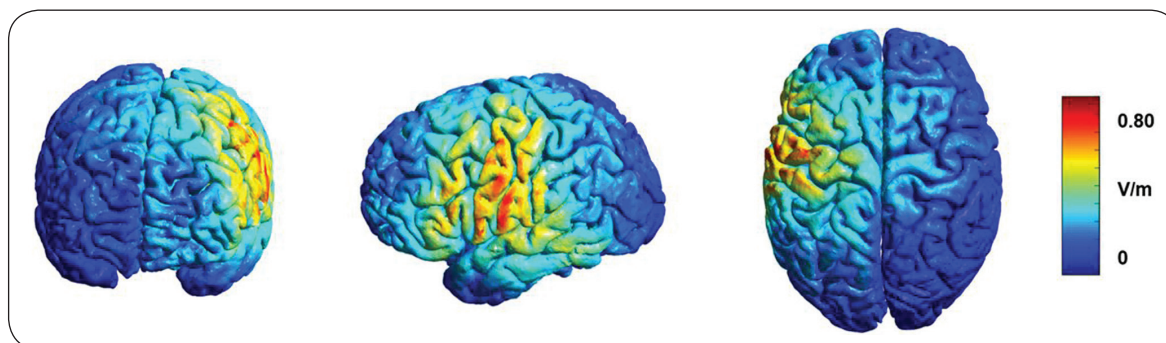
The STARTS study will be one of the largest trials to date assessing the efficacy of tDCS for the treatment of schizophrenia. Our protocol consists of 10 sessions of

tDCS using 2 mA for 20 min, with two sessions a day, similar to the protocol used by Brunelin et al.<sup>56</sup> Sample size was calculated to avoid type I and II errors and can accommodate an attrition rate of 15%. We will enroll patients with different degrees of refractoriness and variable antipsychotic medication treatments, which will significantly increase the external validity of our results. These data could contribute to the analysis of some predictors of response as well.

This trial differs from the clinical trial conducted by Brunelin et al. in several ways, including a larger sample size (100 vs. 30). We are also collecting blood samples and evaluating several additional parameters and biomarkers related to genetics, neuropsychological state, and motor excitability. We will assess depressive symptoms, medication use, and other possible variables that may influence the results, and we are using multiple scales to assess the negative symptoms (SANS).



**Figure 1** - Transcranial direct current stimulation (tDCS) electrode montage for the STARTS clinical trial. The orange electrode placed over the participant's left frontal region corresponds to the anode (A), and the white electrode placed over the left temporoparietal region corresponds to the cathode (C).



**Figure 2** - Simulation of the electric field in the cortex generated by the transcranial direct current stimulation (tDCS) montage to be employed in the STARTS clinical trial.

## Conclusion

The STARTS study will investigate the efficacy of tDCS for the treatment of the negative symptoms of schizophrenia using a randomized, sham-controlled design. The biomarker investigation will contribute to the understanding of the neurobiological mechanisms of schizophrenia and their relationship with treatment. This trial will contribute valuable information to the treatment of schizophrenia.

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## Disclosure

No conflicts of interest declared concerning the publication of this article.

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