ORIGINAL ARTICLE

Comparison of Two Electrode Placement Methods in Transcranial Direct Current Stimulation for Parkinson's Disease

Mohammad Mahdi Moeini Kouchaksaraei, Fereidoun Nowshiravan Rahatabad *, Ali Sheikhani

Department of Biomedical Engineering, Science and Research Branch, Islamic Azad University, Tehran, Iran

*Corresponding Author: Fereidoun Nowshiravan Rahatabad
Email: nooshiravan@gmail.com

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Abstract

Purpose: Therapeutic electrical stimulation of deep brain structures, such as the subthalamic nucleus and the Globus Pallidus (GP), is widely accepted as a treatment tool for patients with Parkinson's Disease (PD). Electrical stimulation of the cerebral cortex with electrodes or transcranial stimulation can increase motor function among PD patients. The present study aimed to evaluate the effects of non-invasive cortical stimulation with simulation of transcranial Direct Current Stimulation (tDCS) technique on parts of the basal ganglia among PD patients.

Materials and Methods: tDCS was simulated using two different electrode placement methods (anodal stimulation of the primary motor cortex (M1) and anodal stimulation of the Dorsolateral Prefrontal Cortex (DLPFC)) and We evaluated the excitation procedure in the target area based on the excitation current distribution in GP and Subthalamic Nucleus according to the patient's condition in both electrode methods. All simulations were performed using head Magnetic Resonance Imaging (MRI) images of four people with PD. Also, according to the excitation current distribution obtained from the previous step, we studied how the excitation current distributed in the target areas is affected by using a model of the basal ganglia so that based on the membrane potential of each excitation in these areas, in all four patients, we compare both electrode-installation methods in a functional way. The effectiveness of brain stimulation was also studied using a basal ganglia model. Considering the membrane potential of GP and Subthalamic Nucleus regions, the effectiveness of each electrode placement method was evaluated in the Basal Ganglia (BG) model.

Results: According to the results, direct current stimulation was propagated through electrodes placed on the scalp throughout the model. Also, anodal stimulation of the M1 had a better stimulation of GP and subthalamic nucleus than anodal stimulation of the DLPFC.

Conclusion: Although, the procedures for performing tDCS and invasive brain stimulation in PD are different, the results show that this treatment can be appropriate and improve motor function in patients with PD.

Keywords: Parkinson's Disease; Transcranial Direct Current Stimulation; Globus Pallidus; Subthalamic Nucleus; Basal Ganglia; 3 Dimensional Model of Brain.

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1. Introduction

Despite many advances in the drug-based treatment of neurological disorders over recent decades, there have been special limitations in the use of this type of treatment such as resistance to certain drugs or adverse complications [1]. Today, there are increasing studies on the treatment of cortical stimuli to improve motor function in Parkinson's Disease (PD) [2-4]. Compared to drug therapies, brain stimulation can have fewer complications and it is able to restore a great deal of balance to parts of the nervous system that are out of balance [1, 5].

Treatments such as functional neurosurgery can effectively improve motor function in PD patients but, conversely, can reverse dyskinesias [6]. Although advances in invasive brain stimulation techniques for PD, such as Deep Brain Stimulation (DBS), have reduced the risks of invasive neurosurgery techniques, due to their invasiveness and complications, they also have disadvantages such as pain and swelling at the implant site, allergic reflexes to implants, intracerebral hemorrhage, infection and inflammation of the meninges, speech and vision problems, itching and burning sensation in the face and limbs, etc. [7]. Therefore, new approaches such as electrical and transcranial stimulation, due to their non-invasive nature, can be more effective than other methods. In addition, unlike DBS, which is used only in cases where drug therapies cannot be effective, non-invasive stimulation methods can be used simultaneously with other treatments. However, epidural motor cortex stimulation may be a valuable method to improve symptoms in PD patients [8-10].

Generally, electrical stimulation on a nerve fiber can generate an action potential. In this state, the voltage or the stimulation current should be larger than the cell membrane stimulation voltage (high threshold stimulation). In another approach, the nerve membrane voltage should be altered in such a way that, without creating action potential the conditions would change so that the stimulation threshold changes (subthreshold stimulation). In this way, cell excitability can be enhanced or reduced. In this state, the transcranial Direct Current Stimulation (tDCS) is a noninvasive and subthreshold stimulation to establish suitable conditions for changing the neuronal excitability, which generally uses two large planar electrodes and a multi-ampere electric current [11].

A major barrier to using non-invasive brain stimulation is limited penetration to regions of the cerebral cortex [12]. Therefore, deep structures such as the basal ganglia cannot be directly and separately targeted. Another major problem of this method is the difference in the effectiveness of this type of electrical stimulation with different electrode placement methods [13, 14]. In this regard, one of the main tools to answer this question is to understand the current distribution in the head due to the difference in the electrode shape in the formation of the electrical field [15].

Although according to clinical studies and medically, tDCS methods have been explored in Parkinson's patients, so far, its degree of effectiveness based on effective parameters such as individual anatomy has not been examined precisely in terms of engineering [16]. Thus, modeling and comparing transcranial Random Noise Stimulation (tRNS) and tDCS can be a massive step in understanding the non-invasive treatment of PD. Nevertheless, in all-new simulations and studies, the physics of brain tissues of every individual has not been considered in calculating the electric current distribution in the head. The structure and thickness of the skull, structural differences of the brain cortex gyri and sulci, and the arrangement of brain cells can affect the size of the current and its distribution across the brain. Accordingly, in the case of applying the same stimulation, different current distribution across individuals is not unexpected, and in turn, the extent of influence of stimulation on anyone can be different [17-22].

Here, we study the effects of two different cortical stimulation techniques of tDCS on Basal Ganglia (BG) stimulation in PD patients. In tDCS, the cerebral cortex is stimulated non-invasively and painlessly through a weak DC current. Many studies have shown that this method is effective in the stimulation of the cerebral cortex in the motor cortex and human vision. Besides, recent research has shown that tDCS can improve some aspects of cognition and improvement of motor impairment in some diseases [23-32].

2. Materials and Methods

2.1. Head model

In collaboration with Parkinson's Progression Markers Initiative (PPMI, RRID:SCR_006431), head Magnetic Resonance Imaging (MRI) images were taken from four

men aged 47 to 68 years with PD. All these images were in the form of "AX, T2, AC-PC line Entire Brain". The imaging protocol is shown in Table 1.

Table 1. Imaging Protocol

Acquisition Plane	AXIAL
Field Strength	3.0 tesla
Manufacturer	GE MEDICAL SYSTEMS
Slice Thickness	2.0 mm
Weighting	T2

MRI images of each patient were segmented into 6 main parts with SPM software. After the MRI image segmentation, the 3D head model was designed using the Simpleware software suite (ScanCAD, ScanFE, ScanIP). To this end, a 3D head model of the head, including the scalp, skull, cerebrospinal fluid, gray matter, white matter, and BG, was fabricated and meshed. In addition, as shown in Figure 1, two electrodes for two different electrode placement methods with conductive gel were placed on the scalp of all four models (a: anodal stimulation of the primary motor cortex (M1) and b: anodal stimulation of the dorsolateral prefrontal cortex (DLPFC)). The size of each electrode was 35 cm^2 [16, 33-37].

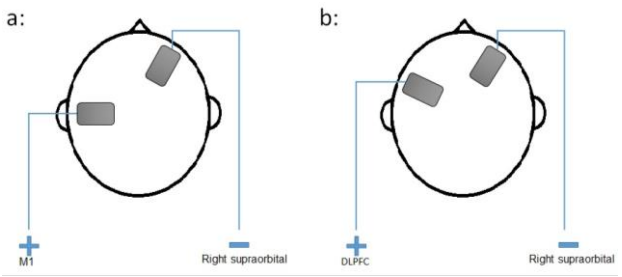

Figure 1. Electrode placement. a) anodal stimulation of the primary motor cortex (M1) and Right supraorbital, b) anodal stimulation of the Dorsolateral Prefrontal Cortex (DLPFC) and Right supraorbital

2.2. tDCS

Cortical electrical simulations were performed for both anodal stimulations of M1 and DLPFC in all four patients using COMSOL software. Accordingly, after entering the model designed in COMSOL, the electrical conductivity of brain tissue for each part of the head was determined according to reference articles [12, 38, 39]. The amount of electrical current in both tDCS methods is equal to 2 mA. The cathode electrode was also placed in the right supraorbital region. After stimulation, the current distribution in the two regions of GP and subthalamic nucleus of the BG was investigated to compare the effectiveness of both methods in these regions [16, 33-37].

2.3. Basal ganglia model

In this part of our simulations in MATLAB software, the basal ganglia-thalamic network model developed by Rubin and Terman (RT model) has been used, which has been improved by Rosa *et al.* [40, 41]. This BG model is composed of Thalamic (TH), Subthalamic Nucleus (STN), and external and internal GP (GPe and GPi) and forms a network that responds to the input of the Sensorimotor Cortex (SMC). Each part of the model consists of 100 nerve cells.

Membrane potential outputs in the BG region of the head stimulation model were used as the stimulation input in this region of the BG model. Accordingly, simulations were performed twice, first when the person was healthy and, second, when the person had PD. Model changes from healthy to PD were achieved by reducing currents applied to STN, GPe, and Gpi [40, 41]. In the last stage, the simulation was performed for a patient who had undergone cerebral electrical stimulation. The comparison of the second and third cases shows the effect of the current distribution in the patient and the comparison of the first and third cases shows the quality of this effect.

3. Results

3.1. Current Distribution in tDCS

According to the head model designed for four different patients in two electrode placement states, as shown in Figure 2, direct current stimulation was simulated through electrodes placed on the scalp in COMSOL software (RRID: SCR_014767).

According to the outputs of the stimulation model, the electrical current is distributed in the target regions. However, there were differences in amount of outputs in the two electrode placement states. However, in each state, the results were quite close in all four patients. Overall, it can be said that the current distribution values are higher in the anodal stimulation of M1 than in the anodal stimulation of DLPFC. As shown in Figure 3, this

superiority is present in both the subthalamic nucleus (Figure 3a) and the GP (Figure 3b) regions of the BG.

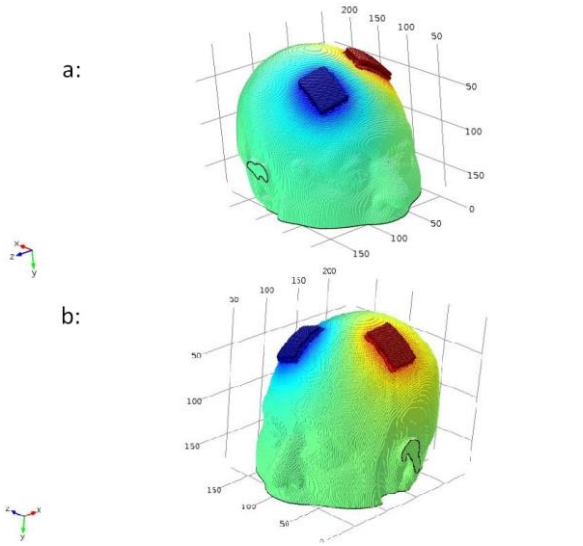

Figure 2. Three-dimensional head stimulation model in two states a) anodal stimulation of DLPFC and b) anodal stimulation of M1 and placement of cathode electrode on right supraorbital region

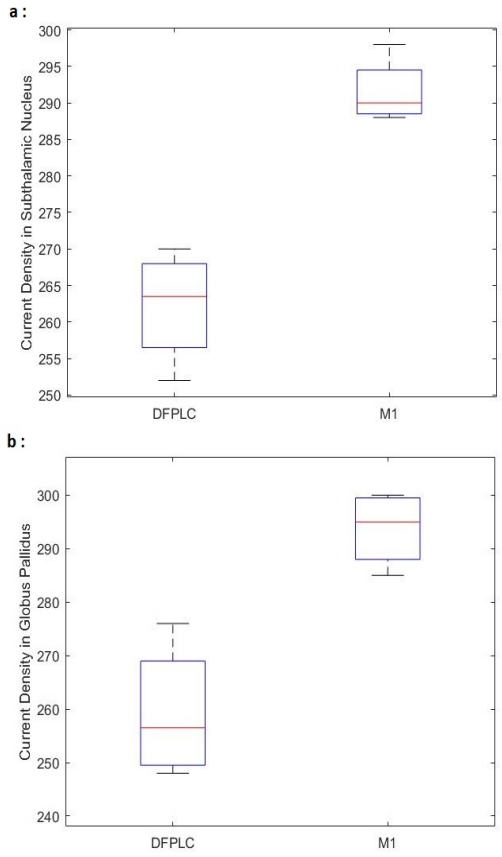

Figure 3. Distribution of the stimulation current in anodal stimulation of M1 and DLPFC according to the results of four patients in two regions a) Subthalamic nucleus and b) Globus pallidus

3.2. tDCS in the Basal Ganglia Model

Based on the model, first, the simulations were performed in a healthy state. As shown in Figure 4a, the outputs were obtained based on the membrane potentials of the thalamic, GP, and subthalamic nucleus regions. Then, the same outputs were simulated in the PD state in the second step (Figure 4b). As can be seen, disturbances in the membrane potential output of the BG regions occur in this case.

In the third step, the outputs of the target regions of the head stimulation model were used as the stimulation input in the PD state in order to calculate the effect of this stimulation method on the membrane potential of the target regions. This step was performed for both electrode placement methods (Figure 5a and Figure 5b).

4. Discussion

In this study, we tried to compare the non-invasive method of direct brain current stimulation based on two different methods of electrode placement. For this purpose, the current distribution in the target areas was investigated by simulation of stimulation on models designed from MRI images of four PD patients. Meanwhile, we compared electrical stimulation in the areas below the electrodes, skull, cerebrospinal fluid, gray matter, and white matter in both electrode placement methods in tDCS. Nevertheless, with respect to the target region in PD, conclusions were drawn based on stimulation in the target region of the ganglion base.

According to the obtained results, it can be said that the stimulation current applied through the electrodes placed on the scalp is completely distributed in the head, especially in the target regions in the basal ganglia. However, the output value was different in the two electrode placement methods. In addition, these numbers were different in all four Parkinson's patients in each method. However, according to the overall results of all four patients shown in Figure 3, anodal stimulation of M1 showed a higher current distribution than anodal stimulation of DLPFC.

In order to better evaluate the effectiveness of tDCS in two different electrode placement methods, the basal ganglia-thalamic network model developed by Rubin and Terman (RT model) was used. Membrane potential outputs from the thalamic, GP, and subthalamic nucleus

regions (Figure 5a and Figure 5b) show that both electrode placement methods can affect our target regions in the basal ganglia. In general, it can be said that both electrode placement methods have acceptable effects on the target regions. However, as expected from the results of the previous section, the anodal stimulation of the M1 method was slightly more effective than the anodal stimulation of DLPFC method. Note that since the BG model was simulated once in a healthy state and another time in a PD state, a comparison of the results of the two stimulation methods with both healthy and PD states indicated the effect of the stimulation methods considering the changes in the model status. It can be stated that the results obtained from the simulation of this stage confirmed the findings obtained from simulations of the previous stage.

The results of this study are in agreement with the results of other studies performed on tDCS techniques in PD [16, 33-37]. Of course, all of these studies have been performed clinically and given the limitations of clinical studies to accurately examine the areas inside the brain, in this study, it has been tried to model the brain images of Parkinson's patients to examine the current distribution in the head and in the target areas. However, there were some limitations in this study. The two main limitations in this study were the number of patients and the duration of the simulation. Considering the complexities of three-dimensional brain simulations, the high calculation time and the heavy volume of information obtained from the model results, it was not possible to significantly increase the number of MRI images of Parkinson's patients. For this purpose, standard images of four Parkinson's patients were used to build three-dimensional models. Due to the condition of PD, it was not possible to take brain images before the disease in a healthy state. Therefore, all images are related to the time when four patients were at a certain level of PD. Also, like other studies on brain models, due to the limitations of simulation and the high volume of calculations related to the three-dimensional model, it was not possible to equate the duration of the simulation with the duration of clinical treatment. But as shown in the results, at the same time the result obtained was quite acceptable and described and generalized clinically.

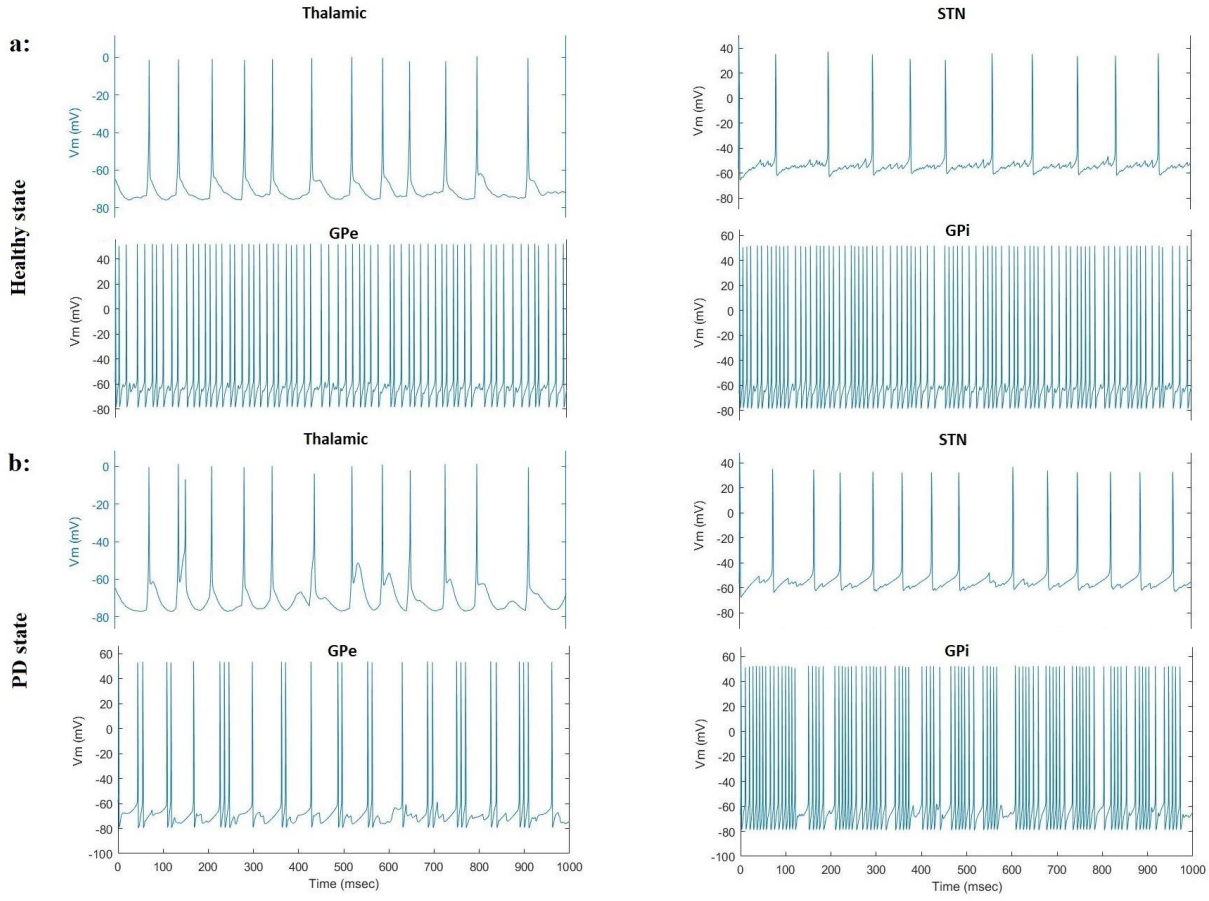

Figure 4. Membrane potentials outputs from the basal ganglia model in the healthy state (a) and PD state (b)

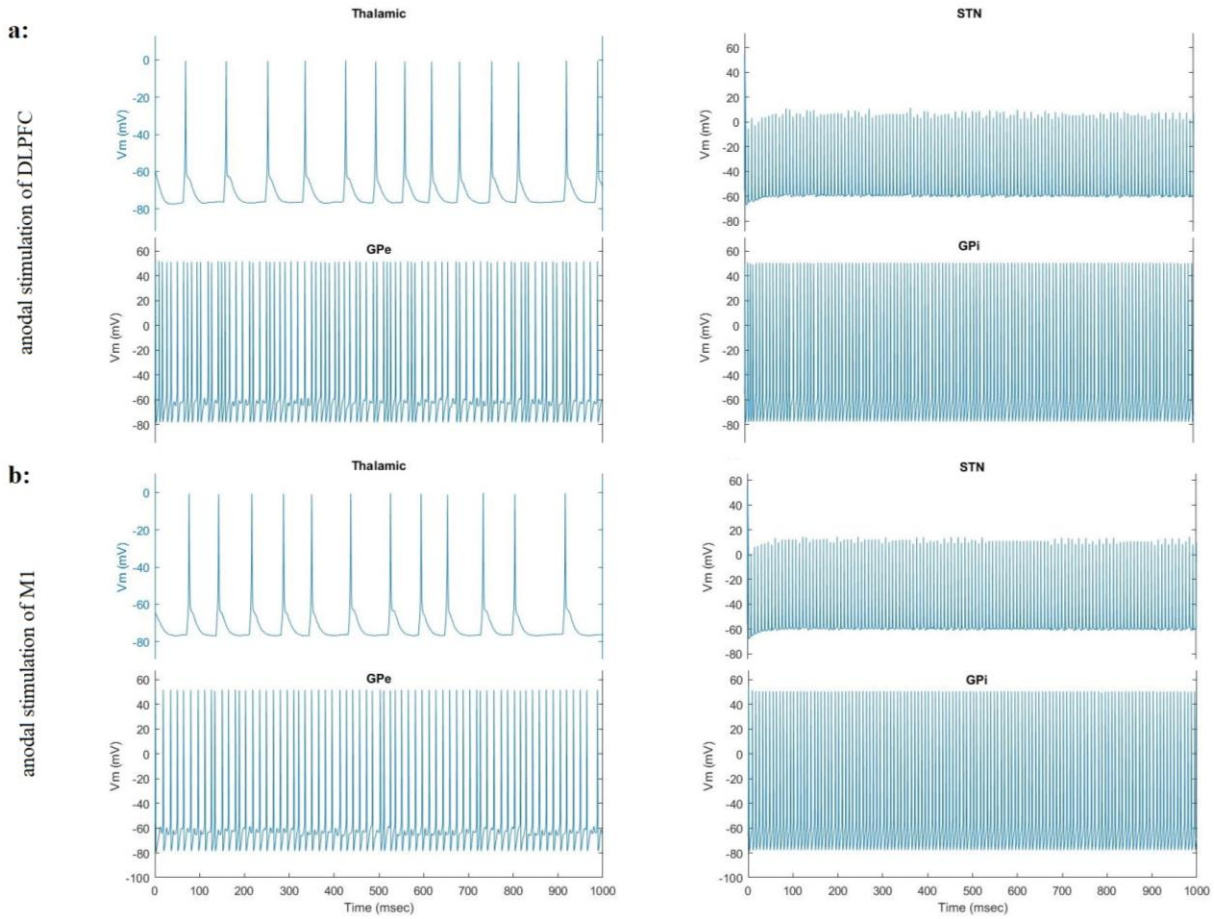

Figure 5. Membrane potentials outputs from the basal ganglia model of a Parkinson's patient in anodal stimulation of DLPFC (a) and anodal stimulation of M1 (b)

5.Conclusion

Given the problems and complications of treatment and management methods through invasive and medication procedures in PD, the use of effective alternative or non-invasive adjuvant methods can greatly help to improve the patient's conditions [42, 43]. Therefore, The present study aimed to evaluate the effectiveness of tDCS method in the target regions of PD and to compare the same effectiveness in two different electrode placement methods for tDCS. The method of performing tDCS is different from other treatment methods such as the drug method or the DBS method. According to the results of this study, it can be said that due to the effectiveness of the tDCS method, these results indicate the usefulness of tDCS in improving motor function in Parkinson's patients.

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