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Full Length Research Paper

The effect of gender on transcranial direct current stimulation post-treatment results in stroke patients with aphasia

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The therapeutic method of transcranial direct current stimulation (tDCS) has been proposed as a safe complementary neuromodulating technique for improving speech disorders in patients after stroke. In the current study we examined the effect of tDCS over inferior frontal gyrus area in 8 chronic post-stroke aphasic female and male patients (4 female and 4 male). The therapeutic protocol consists of the assessment of picture naming (accuracy) before and immediately after anodal type tDCS (2 mA, 20 min) stimulation-in combination with speech therapy, compared to the control group that only followed speech therapy (8 patients, 4 female and 4 male). The post-treatment values of picture naming (13.76 ± 2.12) after treatment with tDCS and speech therapy were statistically improved in the experimental group compared to the control group (11.14±1.27, p=0.04), where additional statistical significance was recorded in post-treatment values between male and female participants, where female patients presented statistically significant major improvement compared to the male patients (female 14.89±1.96 vs male 12.44±1.32 respectively, p=0.04). Therapeutic session with tDCS can be used as a safe and effective complementary method for the treatment of speech disorders following a stroke, where the female patients seem to present a better response to the treatment.

Keywords: Transcranial direct current stimulation, Speech disorders, Stroke patients, Neurorehabilitation

INTRODUCTION

Scientific community considers transcranial direct current stimulation (tDCS) as a complementary neuromodulating technique for therapeutic use in humans, where the main mechanism of action is the change of spontaneous neuronal activity through direct current delivered on the scalp by superficial electrodes, inducing immediate and post-treatment functional modifications in the brain (Holland and Crinion, 2012). As far the technique of use, a stimulating electrode is placed on the scalp over the area of interest and the reference electrode can be placed on a different body part, like the right arm (Nitsche and Paulus, 2000; Priori et al., 1998). This neuromodulating device is considering-based on previous studies-safe, inducing non frequent -minor adverse effects (Liebetanz et al., 2002; Fregni et al., 2005; Sparing et al., 2008).

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The provoked physiological mechanisms during stimulation with tDCS are different from those responsible for post-treatment effects (Baker et al., 2010; Fertonani et al., 2010; Fridriksson et al., 2011; Kang et al., 2011; You et al., 2011; Vines et al., 2008; Giglia et al., 2011; Nitshe et al., 2008; Okamoto et al., 2004). During stimulation is induced a modulation of the resting membrane potential, while the post-treatment effects are explained by multiple physiological mechanisms, such as the induction of long-term potentiation and/or depression (Schlaug et al., 2008; Gandiga et al., 2006; Cattaneo et al., 2011; Liebetanz et al., 2002; Nitsche et al., 2003). Previous studies indicated that using a NMDA-receptor antagonist, the long-lasting effects of tDCS are abolished and that other drugs (such as GABAergic, dopaminergic and cholinergic) acting on neuronal transmitters, minimize the tDCS effect (Stagg and Nitsche, 2011). According to previous studies, direct current electrical stimulation alternate the protein synthesis (Gartside, 1968) the calcium neuronal influx (Islam et al., 1995; Trollinger et al., 2002), the shape of cytoskeleton (Titushkin and Cho, 2009), the local blood flow and the level of brain oxygenation (Merzagora et al., 2010), and locally the pH (Ardolino et al., 2005).

Aphasia is considered as a combination of speech and language disorders caused by brain damage of various nature (Jordan and Hillis, 2006; Nicholas et al., 1993). Approximately 38% of stroke patients present aphasia, a clinical disorder that is associated with severe limitations in social participation and living (Robey, 1994; Robey, 1998). All these years, speech and language therapy (SLT) for aphasia is predominately based on compensatory strategies or training for lost functions and communication (Nicholas et al., 1993).

The aim of the current study was to evaluate the effect of treatment with tDCS in patients with chronic post-stroke aphasia and to compare the post-treatment results between male and female patients. For the current study, direct current stimulation was applied over the damaged left inferior frontal gyrus areas in eight right handed patients with chronic post-stroke aphasia (4 female and 4 male patients). For the evaluation of the post-treatment results, a computer-controlled picture naming task was used before and immediately after the completion (10 daily sessions) of anodal tDCS and speech/language therapy.

MATERIALS AND METHODS

Participants

Eight chronic stroke patients (aged 58.75±4.32 years, range 49-68 years, 4 female and 4 male) with aphasia participated in the current research. All participants were enrolled at least 6 months after the onset of aphasia due to a stroke. The inclusion criteria for the current study were the following: native Greek speakers, right handed, single first-ever left hemispheric stroke, and primarily clinically diagnosed with aphasia. Prior to the final participation, all patients were evaluated by the same professional speech therapist to determine the type and the severity of aphasia. The exclusion criteria included history of seizure and implanted metal object, as these are considered basic contraindications for the use of tDCS (Cattaneo et al., 2011). From the final inclusion, were also excluded patients who had severely impaired auditory-verbal comprehension or dementia. The study was conducted between February 2016 and July 2017 at Filoktitis Rehabilitation Center (Koropi-Attica, Greece), where all participants underwent a complete neuropsychological evaluation, including a shorter version of Token Test (Ginex et al., 2017; De Renzi and Faglioni, 1978) and a standard language examination currently used at the neurological unit of the center. Participants with Token Test < 8, were excluded (De Renzi and Faglioni, 1978). Tables 1 and 2 summarize the patients' stroke characteristics. From an initial group of 16 patients (8 female and 8 male), in a double-blind manner, patients were randomized and divided into 4 groups of 4 patients, in order to form equivalent-in number- female and male groups. Besides the study coordinator (first author) who performed the tDCS treatments, the speech therapist, the nursing stuff and all patients were blinded to the randomization process, the experimental procedure and the aim of the current study.

Picture naming task

For every picture naming session, participants were asked to name pictures presented on a computer screen from one out of 4 lists (A-D). For the accuracy of naming (the number of picture correctly named in a 20-items list), was given score 1 for a correct response and 0 for an incorrect, ranging between1-20. The items lists were homogeneous for difficulties and were controlled for frequency of use, familiarity, visual complexity, grammatical class and syllable length. Each participant was examined in different lists before and after the completion of the treatment protocol.

tDCS treatment

For the aim of the study, anodal tDCS (2 mA, 20 min in each separate session) was delivered by a constant current electrical stimulator (Soterix Medical NY, USA) connected to a pair of using saline-soaked sponge electrodes (5 cm^2), where the active anodal electrode was placed over the left inferior frontal gyrus areas and the reference electrode was placed on the right shoulder of the patients. For the location of the inferior frontal gyrus area, the international 10-20 electroencephalogram (EEG) system was used. According to the 10-20 EEG system, the left inferior frontal gyrus area is defined as F7 (Okamoto et al., 2004). Participants underwent a total of ten daily sessions, and were evaluated before and immediately after the completion of the treatment. All tDCS sessions, in all female and male patients, were performed by the first author (K.P.).

Speech-language therapy

During the study, all patients underwent speech-language therapy for 20 minutes per day, 5 times per week (total of 10 sessions) and it was conducted one on one by the same speech therapist. The speech-language program was formulated based on each patient's aphasic severity, which was evaluated after stroke at his admission to the rehabilitation center and included free talk, corrections of mistakes in pronunciation, and the phonetic annotation of Greek characters.

The experimental group (4 female and 4 male patients) underwent anodal tDCS over the left inferior frontal gyrus area and language-speech therapy in different therapeutic sessions during the same day. The first session to take place was speech therapy (20 minutes duration) and after an interval of 60 minutes, patients underwent the tDCS treatment (20 minutes duration). The participants and the speech therapist were blinded regarding the type of electrical stimulation and the aim of the study. For each naming session the accuracy in naming 20 pictures from one list, randomly selected out of four homogeneous lists, before and after treatment was measured, where each participant did not receive the same list twice during the study.

The control group (4 female and 4 male patients) underwent only language/speech therapy for a total of 10 therapeutic sessions (20 minutes duration for each single session). The participants and the speech therapist were blinded regarding the aim of the study. Similarly to the experimental groups, for each naming session the accuracy in naming 20 pictures from one list, randomly selected out of four homogeneous lists, before and after treatment was measured. Each participant did not receive the same list twice during the study.

Ethical Approval

The protocol approval was obtained from the clinical human research and ethical review committee at the Kapodestrian University of Athens, School of Medicine (Athens, Greece). The purpose of the current study, potential benefits and/or risks, inconveniences, and the participants' rights and responsibilities were explained in detail to the patients and their family members. After reading the consent form to the participants and family members, a written informed consent (in accordance with the current revision of the Declaration of Helsinki) was obtained from every participant.

Data Analysis

All analyses were performed using the software package SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test revealed that the data were not normally distributed in the present study. For this reason, Wilcoxon signed-rank tests were used to evaluate the differences between accuracy naming before and after therapeutic intervention for each experimental and control group. Baseline values of all groups were analyzed using the Mann-Whitney U test. Statistical significance was considered to be at a level of p=.05.

RESULTS

None of the participants reported severe adverse effects during the electrical stimulation, and they all tolerated the tDCS without interrupting the procedure. Two of the participants (12%), after the completion of the treatment, presented light frontal headache that passed several hours after the procedure, without intake of any analgesic drug.

Before the treatment (baseline values) there was no statistical difference between the 2 groups (experimental and control) in terms of age (experimental group 58.75 years and control group 60.12 years, p=0.06) and time of the onset of aphasia (experimental group 6.28 months vs control group 6.17 months, p=0.07). Similarly, no statistical difference was found between female and male patients of the experimental group in terms of age (female patients 57.82 years vs male patients 58.94 years, p=0.06).

Baseline values (before treatment) in the two groups (experimental and control) did not differ statistically (experimental group 11.12±2.13 vs control group 10.82±2.13, p=0.68). Statistical analysis indicated a statistically significant difference between the baseline and post treatment values in the experimental group (baseline 11.12±2.13 vs post 13.76±2.12, p=0.04). The statistical analysis in the control group indicated a non statistical significance in pre and post-treatment values in the accuracy in naming (before 10.67±2.04, after 11.14±1.27, p=0.82). The post-treatment values of picture naming (14.96 ± 2.41) in female participants of the experimental group were statistically improved compared to the male participants of the same group (female 13.29±1.96 vs male 12.14±1.32, p=0.04), where no statistical significance was found in baseline values between females and males participants of the experimental group (female patients 11.81±2.45 vs male patients 10.83±1.34 respectively, p=0.07).

Table 1. Male patients' stroke characteristics (experimental and control groups)

Patient	Gender (M:male)	Duration of aphasia (months)	Brain lesion	Type of aphasia
1	M	7	left middle cerebral artery infarction	Broca
2	M	6	left basal ganglia infarction	Broca
3	M	8	left middle cerebral artery infarction	Anomic
4	M	6	left basal ganglia infarction	Transcortical motor
5	M	9	left basal ganglia intracerebral hemorrhage	Broca
6	M	7	left basal ganglia infarction	Anomic
7	M	8	left middle cerebral artery infarction	Anomic
8	M	6	left basal ganglia infarction	Broca

Table 2. Female patients' stroke characteristics (experimental and control groups)

Patient	Gender (F:female)	Duration of aphasia (months)	Brain lesion	Type of aphasia
1	F	8	left middle cerebral artery infarction	Anomic
2	F	7	left basal ganglia intracerebral hemorrhage	Broca
3	F	6	left middle cerebral artery infarction	Anomic
4	F	6	left basal ganglia infarction	Broca
5	F	9	left basal ganglia intracerebral hemorrhage	Broca
6	F	6	left basal ganglia infarction	Anomic
7	F	8	left middle cerebral artery infarction	Anomic
8	F	7	left basal ganglia infarction	Transcortical motor

DISCUSSION

In a previous study (Karagounis and Vissarakis, 2017), we evaluated the accuracy of picture naming before and after the completion of anodal tDCS stimulation during speech therapy, compared to tDCS and speech therapy taking place at different times and to the control group that only followed speech therapy. The post-treatment values of picture naming after simultaneous treatment with tDCS and speech therapy in the same therapeutic session, were statistically improved compared to the double treatment at different times and to speech therapy group, resulting that simultaneous therapeutic session with tDCS and speech therapy can be used as a safe and effective interventional method, in place of the conventional speech-language therapy, for the treatment of aphasic patients following a stroke.

In the current research we confirmed the positive effect of tDCS on the treatment of stroke patients with aphasia. In accordance with previous studies (Fregni et al., 2005; Sparing et al., 2008; Baker et al., 2010; Fertonani et al., 2010; Fridriksson et al., 2011; Cattaneo et al., 2011), the tDCS provoked a statistically significant improvement in language recovery, without presence of severe adverse effects. To avoid confusion regarding the source of the observed effect, we used an extracephalic (arm) reference electrode (Monti et al., 2008). In both female and male experimental groups, the post-treatment naming accuracy was improved within a short time of 10 therapeutic days, highlighting the significant role of transcranial direct current stimulation in aphasia's rehabilitation. The current consensus is that two main mechanisms are involved in the recovery from aphasia (Heiss et al., 1999; Heiss and Thiel, 2006). First, in patients with relatively small lesions in the left hemisphere, the recruitment of perilesional cortical neuronal elements plays a critical role in the recovery from aphasia after stroke. Various functional magnetic resonance imaging studies (Karbe et al., 1998; Warburton et al., 1999) have previously demonstrated that greater activation in the left hemisphere is associated with a better outcome for language recovery (Heiss et al., 1999; Heiss and Thiel, 2006; Karbe et al., 1998; Warburton et al., 1999). Thus, the enhancement of the excitability of the left language-related cortical regions by non-invasive brain stimulation may improve recovery from aphasia (Fridriksson et al., 2011).

The participants varied with respect to the subtypes of aphasia, lesion location, and the extent of brain damage. Regardless of the type of aphasia, the role of the left frontal cortex in its recovery has been demonstrated as in previous studies (Karbe et al., 1998; Warburton et al., 1999). A previous functional magnetic resonance imaging study revealed that the activation of the left frontal cortex was correlated with the naming accuracy in stroke patients with aphasia (Fridriksson et al., 2010). Furthermore, increasing the excitability of the left frontal cortex using tDCS improved naming accuracy, irrespective of the subtype of the aphasia, and the extent of the stroke lesion (Baker et al., 2010). The results from our study are consistent with previous reports and confirm that the activation of the left frontal cortex, particularly the left inferior frontal gyrus area, improves naming ability in various types of aphasia (Karbe et al., 1998; Warburton et al., 1999). The traditional speech and language therapy for aphasia is predominately based on compensatory strategies or training for lost functions (Fridriksson et al., 2010). However, the results did not demonstrate any significant change in the naming accuracy after speech therapy. The short experimental period of 10 days could be a reasonable answer for the relative stability in the naming accuracy progress. It seems that the simultaneous activation, via transcranial direct current stimulation and speech therapy, of the corresponding speech areas provokes better results in the rehabilitation of the stroke patients with aphasia.

Regarding the differences in post-treatment improvement between female and male participants, our research is in accordance with previous studies, highlighting the impact of gender on neural excitability. In a recent study (Martin et al., 2017) was investigated if sex mediates the effects of high-definition transcranial direct current stimulation (HD-tDCS) administered to a key hub of the social brain (the dorsomedial prefrontal cortex, dmPFC) on the Reading the Mind in the Eyes Test (RMET). For this purpose, forty healthy young adults (18-35 years) were randomly allocated to receive either anodal or cathodal HD-tDCS in sham HD-tDCS controlled, double blind designs. In each of the two sessions, subjects completed the RMET. Anodal stimulation to the dmPFC increased accuracy on the RMET in females only. This study showed improved performance on the RMET after tDCS to the dmPFC in females only. The polarity-specific effects and use of focal HD-tDCS provided evidence for sex-dependent differences in dmPFC function in relation to the RMET. The authors suggested that future studies using tDCS to study or improve ToM, need to consider sex.

In another study (De Tommaso et al., 2014) was investigated spatial attention by means of a bisection line test and computer-supported attention task during the menstrual cycle in healthy women compared to men, in basal condition and under tDCS of the left parietal cortex. Women were studied during the menses, follicular and luteal phases, ascertained by transvaginal ultrasounds. In basal conditions, women showed a clear deviation toward the right in the bisection line test during the menstrual phase, similarly to men. The midpoint recognition in the computer-supported attention task was not influenced by the menstrual cycle for women, while men showed a significant increase in errors toward the left side. The anodal activation of the left parietal cortex did not affect the line bisection task, while in men it reduced the total amount of errors in midpoint recognition observed in the computer supported attention task. The hand-use effect demonstrated by the bisection-line test could be influenced by estrogen fluctuations, while the right hemisphere prevalence in spatial attention appears to be gender-related and scarcely influenced by the menstrual cycle. The authors referred that the left parietal cortex seems to exert a scarce effect on hand-use effect, while its activation is able to revert sex related right hemisphere supremacy, concluding that sex hormonal variations have been shown to affect functional cerebral asymmetries in cognitive domains, contributing to sex-related differences in functional cerebral organization.

Other researchers (Chaieb et al., 2008) investigated correlations between sex differences with respect to neuroplastic effects. Visual evoked potentials (VEPs), phosphene thresholds (PTs), and contrast sensitivity measurements (CSs) were used as indicators of the excitability of the primary visual cortex. The data revealed that cathodally induced excitability effects 10 minutes post stimulation with tDCS, showed no significant difference between genders. However, stimulation in the anodal direction revealed sex-specific effects: in women, anodal stimulation heightened cortical excitability significantly when compared to the age-matched male subject group. There was no significant difference between male and female subjects immediately after stimulation. These results indicated that sex differences exist within the visual cortex of humans, due to the influences of modulatory neurotransmitters or gonadal hormones which mirror short-term neuroplastic effects.

Additionally, the ion channels and receptors involved in the effects of tDCS were investigated in another study (Nitsche et al., 2003). Thus, the impact of the sodium channel blocker carbamazepine, the calcium channel blocker flunarizine and the NMDA receptor antagonist dextromethorphane on tDCS-elicited motor cortical excitability changes of healthy human subjects were tested. Carbamazepine selectively eliminated the excitability enhancement induced by anodal stimulation during and after tDCS. Flunarizine resulted in similar changes. Antagonising NMDA receptors did not alter current-generated excitability changes during a short stimulation, which elicits no after-effects, but prevented the induction of long-lasting after-effects independent of their direction. These results suggested that cortical excitability shifts induced during tDCS in humans depend on membrane polarisation, thus modulating the conductance of sodium and calcium channels. Moreover, they proposed that the after-effects may be NMDA receptor dependent. Since NMDA receptors are involved in neuroplastic changes, the results suggested a possible application of tDCS in the modulation or induction of these processes. A reasonable explanation for the major improvement in female participants in our study could be a different quality and quantity of sodium/calcium channels and NMDA receptors between female and male patients.

The current study has several limitations, however. First, the excitability of the stimulated cortical area was not examined directly (for example, via functional imaging techniques). Second, the population was relatively small and heterogeneous, and thus, it was not possible to evaluate the effects relative to specific brain lesions or subtypes of aphasia. Third, we did not consider the type of sham activation in the experimental protocol, because of the already existing complexity of the procedure. Further studies on the cumulative and long-term effects of simultaneous tDCS/speech therapy sessions are required for appropriate daily clinical application.

CONCLUSION

In conclusion, we consider that therapeutic intervention with tDCS can be used as a safe and effective complementary method for the treatment of aphasic patients following a stroke. The gender seems to be one of the factors that influence the tDCS post-treatment result, probably due to differences in modulatory neurotransmitters and/or gonadal hormones with neuroplastic effects, that have to be examined in future studies.

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