

Changes in the Sensory Function after Transcranial Direct Stimulation on Dorsolateral Prefrontal Cortex Area

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배외측전두엽피질 영역에 경두개직류전류자극이 감각기능에 미치는 영향

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Abstract Transcranial direct current stimulation (tDCS) is a neuromodulatory technique that delivers a low-intensity direct current to the cortical areas, thereby facilitating or inhibiting spontaneous neuronal activity. This study was designed to examine the changes in various sensory functions after tDCS. A single-center, single-blinded, randomized trial was conducted to determine the effect of a single session (August 4 to August 29) of tDCS with the current perception threshold (CPT) in 50 healthy volunteers. Nerve conduction studies (NCS) were performed in relation to the median sensory and motor nerves on the dominant hand to discriminate peripheral nerve lesions. The subjects received anodal tDCS with 1mA for 15 minutes under two different conditions, with 25 subjects in each group. The conditions were as follows: tDCS on the dorsolateral prefrontal cortex (DLPFC) and sham tDCS on DLPFC. The parameters of the CPT was recorded with a Neurometer[®] at frequencies of 2000, 250 and 5 Hz in the dominant index finger to assess the tactile sense, fast pain and slow pain, respectively. In the test to measure the CPT values of the DLPFC in the anodal tDCS group, the values increased significantly in all of 250 and 5 Hz. All CPT values decreased for the sham tDCS. These results showed that DLPFC anodal tDCS can modulate the sensory perception and pain thresholds in healthy adult volunteers. This study suggests that tDCS may be a useful strategy for treating central neurogenic pain in rehabilitation medicine.

요약 경두개직류전류자극(tDCS)은 낮은 직류 전류 강도를 사용하여 대뇌피질의 자발적인 신경학적 활동의 흥분성을 증가 또는 감소시키는 신경조절 기법이다. 본 연구의 목적은 tDCS를 적용한 후 다양한 감각 기능의 변화를 측정하는데 있다. tDCS의 효과를 측정하기 위해 CPT 검사를 50명의 건강한 대상자에게 단일 기간(8월4일에서 8월29일), 단일 공간, 단일 맹검법으로 무작위 배정하였다. 신경전도검사는 우세 손의 말초신경 병변을 구별하기 위해 정중 감각과 운동신경을 측정하였다. 대상자들은 각 25명 씩 대뇌피질의 DLPFC의 tDCS 자극군과 대뇌피질의 DLPFC의 tDCS 위자극군으로 2개의 다른 조건 아래서 1 mA의 전류강도로 15분씩 양극 tDCS로 적용하였다. 촉각, 빠른 통증과 느린 통증을 각각 평가하기 위해 우세한 제 2수지에 2000, 250, 그리고 5 Hz의 주파수로 CPT 검사인 Neurometer[®]를 이용하여 수치들을 기록하였다. DLPFC의 양극 tDCS 자극군의 CPT 수치들에서는 250과 5 Hz에서 통계적으로 유의한 증가를 보였다. 양극 tDCS 위자극군의 모든 CPT 수치들은 감소하였다. 이러한 결과는 DLPFC의 양극 tDCS가 건강한 대상자들의 감각 지각과 통증 역치들을 조절할 수 있다는 것을 보여준다. 따라서 본 연구는 재활과 통증 치료 분야에서 유용한 치료 방법 중 하나로 제시할 수 있을 것으로 생각한다.

Key Words : Current perception threshold(CPT), Dorsolateral prefrontal cortex(DLPFC), Sensory function, Transcranial direct current stimulation(tDCS)

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1. Introduction

Non-invasive methods of brain stimulation, including transcranial direct current stimulation(tDCS) and repetitive transcranial magnetic stimulation(rTMS), are emerging as promising techniques for the management of pain in patients[1]. Among these, tDCS is simple to apply and selectively induces and continues functional changes in the cerebral cortex. Its mechanism is one whereby the electrical field passes through the scalp and the skull, and controls the excitability of the cerebral cortex, thereby changing brain functions. This has been used for research in diverse areas[2]. tDCS has contrasting effects according to polarity: anodal stimulation increases excitability of the cerebral cortex and cathodal stimulation decreases it[3]. Such an increase or decrease in excitability may differ according to the intensity of stimulation, the location of electrodes, and the direction of the corresponding electrical field[4,5]. The method currently in general use, when applying tDCS, use a current intensity of 1 to 2 mA, electrode size of 25 to 35 cm², and a stimulation time of 20 to 30 minutes[6-8]. Its side effects many include slight stinging, headache, fatigue, and nausea, but they are relieved soon after stimulation and do not continue [8,9]. Recent, research into decision making[10], language[11], memory[12], and pain[13] has investigated the clinical application of tDCS. These researchers have reported the effects of cerebral cortex control through diverse neural networks. In particular, tDCS is used as an excellent means for enhancing mood and anxiety in patients suffering from depression, and also to control chronic pain[14] in patients with traumatic spinal cord injury[15], fibromyalgia[16], and cancer[17]. There has been much research, in various fields, into the effects of applying tDCS, but most of the research into sensory functions, dealing with pain and its mechanisms, has not been verified. Boggio et al. applied anodal tDCS to different cerebral cortex areas of healthy adults and reported that the perception and pain thresholds in the

primary motor cortex(MI) and only the pain thresholds in the dorsolateral prefrontal cortex(DLPFC) increased[18].

The current perception threshold(CPT) test is a quantitative sensory function test and may be applied to patients without discomfort and within a relatively short time compared to other existing tests. This test selectively stimulates the peripheral nervous fibers--the large myelinated nerve A β , small myelinated nerve A δ , and unmyelinated nerve C in the form of a sine curve at 2000 Hz, 250 Hz, and 5 Hz. It is possible to quantify the sensory threshold by electrical stimulation through the skin with three different frequencies, and therefore the test is used for diagnosis of various neuropathies, including peripheral neuropathy[19,20]. Kodama et al. examined changes in the thresholds of A β , A δ , and C by applying the CPT test to the MI, and the somatosensory evoked potentials(SEPs) test to the S1 using low frequency rTMS. According to the CPT test of the MI, the thresholds of A β , A δ , and C all increased, and excitability of the S1 was inhibited in the SEPs[21]. To date, diverse studies have measured sensory changes after the application of tDCS but there has been no study that investigated changes in each sensory nerve as Kodama et al.[21] did. Therefore, this study applied tDCS to the MI of the cerebral cortex and measured changes in the peripheral sensory nerves, thereby clarifying the effects of tDCS on sensory nerves and providing evidential material for its clinical application.

2. Materials and Methods

2.1 Subjects

The subjects were healthy, right-handed adults who did not have a history of brain damage or neurological abnormality, and did not exhibit any problem in electroneurography. The number of subjects was 50(male:37, female:13) and they were equally and randomly assigned to either a tDCS group or a sham

tDCS group. Experimental period proceeded from August 4 to August 29. Sufficient explanation was given to them and a written consent was obtained from them.

2.2 Methods

2.2.1 Electroneurography

All the subjects received electroneurography (Kennewick, Washington, USA). Electroneurography was conducted prior to the CPT test in order to verify whether the subjects' right upper extremity sensory nerves were normal. For the electroneurography, median nerves among the right upper extremity sensory nerves were measured in an examination room where the temperature was maintained at between 26 and 28 °C (skin temperature: 30 to 32 °C) according to the method presented by Liverson and Ma[6]. Amplitudes and latencies of the sensory nerves were recorded.

2.2.2 CPT Test

CPT values of all subjects were calculated prior to the application of tDCS. The CPT test was conducted with a Neurometer[®] (Neurotron, Baltimore, USA). The subjects sat comfortably on a chair, a thin layer of conductive gel was applied, and then a pair of gold electrodes was attached with an unstretched tape to the distal part of the distal interphalangeal joint of the second finger (Figure 1). The subjects were randomly and equally assigned to a control group or to an experimental group, and then the CPT values were measured in a single blind-method and in manual mode. A current with frequencies of 2000 Hz, 250 Hz, 5 Hz was applied to the subjects with an intensity of stimulation starting from 0.001 mA, until the subjects felt the electrical current for the first time. The stimulation intensity ranged from 0.001 mA to 9.99 mA. When the subjects felt electrical current, the stimulation was turned off. The intensity was then lowered to 100 μ A, another stimulation was given, and the threshold values were checked. Stimulation was given again within an error margin of 20 μ A to measure

the threshold values. CPT values were repetitively measured to obtain a constant result. When the same result occurred twice, consecutively, the value was considered as the threshold of the subject. After applying tDCS to all the subjects, CPT values were measured again, using the method described above.



[Fig. 1] (A) Method of current perception threshold test. (B) A Neurometer[®] CPT/C was used to measure current perception threshold (CPT) values at frequencies of 2000, 250, and 5 Hz in the right finger to assess the tactile sense, fast pain, and slow pain, respectively.

2.2.3 tDCS

The tDCS device, Phoresor II Auto (PM850, IOMED[®], Salt Lake City, Utah, USA) was used. The size of the two sponge electrodes attached to the scalp was 25 cm² (5cmx5cm) and their current density was 0.08mA/cm². The electrodes were soaked with 0.9% physiological saline and attached to the subjects as tightly as possible, but to an extent at which the subjects did not feel discomfort. The positive electrode was attached to the DLPFC corresponding to the F3 location whose reliability had been verified by neuronavigational techniques[22,23] and the negative electrode was attached to the upper part of the opposite orbital region (Figure 2). In the anodal tDCS group, current intensity and stimulation time were set at 1 mA and 15 minutes, respectively. In the sham tDCS group, the electrodes were attached to the DLPFC in the same way as for the tDCS group. After giving 1 mA stimulation that could be perceived for 30 seconds, the

stimulation was removed. The sham group subjects remained in the same position at rest as the tDCS group with the electrodes attached for 15 minutes. Such an experimental procedure has been proven in recent research to be an efficient blind method[24].



[Fig. 2] The equipment for the tDCS and stimulation targets. For the anodal stimulation (+) of DLPFC, the anode electrode was placed over F3 and the cathode electrode (-) was placed over the contralateral supraorbital area. For the sham stimulation, the electrodes were placed in the same positions as for anodal DLPFC. The stimulator was turned off after 30s of stimulation.

2.3 Statistical Analysis

In this study, statistical analysis was conducted with SPSS 19.0K for windows (SPSS Inc, Chicago, IL, USA) and as a normality test the Kolmogorov-Smirnov/Shapiro-Wilk test was carried out. A paired t-test was performed to compare the DLPFC between, prior to, and after the intervention in the tDCS group and the sham tDCS group. A statistical significance level was set at $p < .05$.

3. Results

3.1 Demographic and Clinical Characteristics of the Subjects

There were no statistically significant differences in age, height, and weight between the tDCS group and the sham tDCS group ($p > .05$), and electroneurography of the right upper extremity nerves also showed no

statistically significant differences in amplitude or latencies between the groups ($p > .05$); Prior to the experiment, there were no differences in the clinical characteristics of the tDCS group (Table 1).

3.2 Comparison of CPT Values of the DLPFC between tDCS and Sham tDCS Groups

In the test to measure CPT values of the DLPFC in the tDCS group, the values of the distal part of the distal interphalangeal joint of the second finger increased in all of 2000 Hz, 250 Hz, and 5 Hz ($p < .05$). Such increase was statistically significant in 250 Hz and 5 Hz ($p < .05$) but not in 2000 Hz. On the contrary, in the sham tDCS group, the values decreased in all of 2000 Hz, 250 Hz, and 5 Hz, which was not statistically significant, however (Table 2).

[Table 1] Demographic and Clinical Characteristics of the Subjects

	Stimulation Group	Sham Group	p-value
Number	25	25	
Age (yr)	22.5±3.3	21.9±1.9	.48
Male	17	20	
Female	8	5	
Height (cm)	168.4±7.6	170.6±7.1	.27
Weight (kg)	65.1±13.0	63.50±10.3	.59
NCS			
amplitude (mV)	36.3±14.8	34.3±10.3	.54
latency (ms)	2.2±0.2	2.2±0.2	.83

mean±standard deviation.

NCS; Nerve conduction study.

[Table 2] Comparison of Pre-test and Post-test CPT Values in the tDCS and Sham tDCS Groups

	DLPFC Stimulation Group			DLPFC Sham Group		
	2kHz	250Hz	5Hz	2kHz	250Hz	5Hz
Pre	270.7±56.8	125.4±72.2	151.5±97.9	272.7±57.8	127.8±79.5	177.7±122.3
Post	284.1±61.5	150.4±71.0	162.8±95.5	252.0±64.4	115.7±60.0	132.7±78.3
p value	0.08	0.01*	0.03*	0.13	0.51	0.31

mean ± standard deviation. * $p < .05$

4. Discussion

The DLPFC area of the cerebral cortex is closely associated with discomfort from pain, anxiety[25], and depression[26] and plays an important role in emotional regulation of pain by actively controlling pain perception through the cortico-subcortical and cortico-cortical pathways[27]. Previous research examined somatosensory perception of pain in the DLPFC area[25,28,29] and its role in emotional control[30]. In the present study, tDCS resulted in significant increase in the values at 250 Hz and 5 Hz, which means that the overall thresholds of nerve fibers A δ and C, in other words, small nerve fibers engaging in fast pain, slow pain, cold sense, and warm sense went up. In the present study, changes in nerve fibers related to pain control were able to be observed to compare it with previous studies. The DLPFC area is considered to have relation with pain by central nervous system mechanism such as phantom pain or complex regional pain syndrome type 1. Boggio et al[31] applied anodal tDCS with 2 mA current and sham tDCS for five minutes to each area of the cerebral cortex(the MI, DLPFC, occipital cortex) and there was significant decrease in displeasure and discomfort in the DLPFC area only. Although the stimulation intensity and application time of their study differ from those of the present study, they were able to find common neurological changes through tDCS. It is considered that there exists the effect of stimulating the DLPFC under the general, mainly used method to apply tDCS where current intensity is 1 to 2 mA, electrode size 25 to 35cm², and stimulation time 20 to 30 minutes. In a study by Liu et al[32], fentanil pain killer was intravenously and extradurally administered and then the CPT test was performed; The threshold increased at 250 Hz and 5 Hz when the drug was intravenously administered and at 5 Hz when it was extradurally administered. The present study as well verified that application of tDCS to the DLPFC resulted in a similar outcome, which may present the

mechanism of pain control. Under high-frequency rTMS, another non-invasive brain stimulation technique, application of tDCS to the left DLPFC area of depression patients led to decreased pain[26]. Boggio et al[18] applied anodal tDCS to the diverse cerebral cortex areas of healthy adults with 2 mA current for five minutes and measured their peripheral electrical stimulation; The result was only the pain threshold significantly rose in the DLPFC area. Their study applied dual tDCS to the MI and DLPFC and presented its simultaneous effects of decreasing discomfort and pain in chronic spinal cord damage patients. The present study as well obtained a statistically significant result of tDCS application to the MI and DLPFC in the CPT test, clarifying the ground for clinical use of tDCS for patients with pain. This study examined changes in each sensory nerve fiber through a CPT test that had not been inquired into in previous research, providing a ground to clarify sensory the function control mechanism of tDCS stimulation and its effects.

In the sham tDCS group, the thresholds of the DLPFC all decreased. In previous studies, the sham tDCS group did not experience any change--with no excitability of the cerebral cortex or decrease in the threshold. In contrast, in the present study, although CPT values did not significantly go down when each area was stimulated, clinically, sensitivity improved. In a preliminary study, prior to the present study, the sensory threshold test was conducted again, after taking a rest for 15 minutes in a quiet environment without stimulation, and the same finding was observed. This is considered to be because of due to the effects of stability and retest rather than the effects of a placebo or stimulation. Such a result is a limitation of this study. Therefore, consistency among researchers in the environmental conditions of the sham stimulation group is considered necessary. In addition, observation of the carry-over effect in patients with the same sensitivity needs to be achieved by applying both stimulation and sham stimulation to the same patients. Much research is being performed

on diverse application areas and effects of tDCS. This study measured changes according to tDCS stimulation and the kinds of peripheral sensory nerve fibers, thereby laying the clinical foundations for application of tDCS to treatment of pain through different mechanisms. tDCS may be presented as one of the useful treatment methods in rehabilitation and pain treatment.

5. Conclusion

This study applied tDCS to the DLPFC, and measured changes in the peripheral sensory nerves, thereby investigating the effects of tDCS on sensory nerves, and providing supportive materials for its clinical use. The healthy subjects were divided into an anodal tDCS group and a sham tDCS group for application of tDCS. The CPT values in A δ and C nerve fibers of the DLPFC increased statistically significantly in the tDCS group. Although CPT values in the sham tDCS group decreased in the DLPFC, such decreases were not statistically significant. These results showed that tDCS had significantly different effects on each nerve fiber, according to the stimulation location of the cerebral cortex. For active clinical application of tDCS, a follow-up study into the mechanism of change in the sensory functional system, the effects according to stimulation intensity and time, and temporal indications is considered necessary.

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<Research Interests>

Brain stimulation