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Changes in Sensory Function After Transcranial Direct Current Stimulation on Primary Motor Cortex Area

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Abstract

Transcranial direct current stimulation (tDCS) is a neuromodulatory technique that delivers low-intensity direct current to cortical areas, thereby facilitating or inhibiting spontaneous neuronal activity. This study was designed to investigate changes in various sensory functions after tDCS. We conducted a single-center, single-blinded, randomized trial to determine the effect of a single session of tDCS with the current perception threshold (CPT) in 50 healthy volunteers. Nerve conduction studies 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 1 ㎃ for 15 minutes under two different conditions, with 25 subjects in each groups: the conditions were as follows tDCS on the primary motor cortex (M1) and sham tDCS on M1. We recorded the parameters of the CPT a with Neurometer® at frequencies of 2000, 250, and 5 ㎐ in the dominant index finger to assess the tactile sense, fast pain and slow pain, respectively. In the test to measure CPT values of the M1 in the tDCS group, the values of the distal part of the distal interphalangeal joint of the second finger statistically increased in all of 2000 ㎐ (p=.000), 250 ㎐ (p=.002), and 5 ㎐ (p=.008). However, the values of the sham tDCS group decreased in all of 2000 ㎐ (p=.285), 250 ㎐ (p=.552), and 5 ㎐ (p=.062), and were not statistically significant. These results show that M1 anodal tDCS can modulate sensory perception and pain thresholds in healthy adult volunteers. The study suggests that tDCS may be a useful strategy for treating central neurogenic pain in rehabilitation medicine.

Key Words: Current perception threshold; Primary motor cortex area; Sensory function; Transcranial direct current stimulation.

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 (Fregni et al, 2007). 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 the controls excitability of the cerebral cortex, thereby changing brain functions. This has been used for research in diverse areas (Wagner et al, 2007). tDCS has contrasting effects according to polarity: anodal stimulation increases excitability of the cerebral cortex and cathodal stimulation decreases it (Vines et al, 2008). 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 (Nitsche and Paulus, 2001; Priori et al, 1998). The method currently in general use, when applying tDCS uses a current intensity of 1 to 2 ㎃, electrode size of 25 to 35 ㎠, and a stimulation time of 20 to 30 minutes (Iyer et al, 2005; Nitsche and Paulus, 2000; Poreisz et al, 2007). Its side effects may include slight stinging, headache, fatigue, and nausea

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but they are relieved soon after stimulation and do not continue (Antal et al, 2007; Poreisz et al, 2007). Recent, research into decision making (Fecteau et al, 2007), language (Flöel et al, 2008), memory (Fregni et al, 2005), and pain (Fregni et al, 2007) 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 (Boggio et al, 2008) in patients with traumatic spinal cord injury (Fregni et al, 2006b), fibromyalgia (Fregni et al, 2006a), and cancer (Silva et al, 2007). 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 (2008) applied anodal tDCS to different cerebral cortex areas of healthy adults, and reported that the perception and pain threshold in the primary motor cortex (M1) and the pain threshold only in the dorsolateral prefrontal cortex (DLPFC) increased.

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 Aβ, small myelinated nerve Aδ, 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 (Katims et al, 1987). Kodama et al (2009) examined changes in the thresholds of Aβ, Aδ, and C by applying the CPT test to the M1, and the somatosensory evoked potentials (SEPs) test to the primary sensory cortex (S1), using low frequency rTMS. According to the CPT test of the M1, thresholds of Aβ, Aδ, and C all increased, and excitability of the S1 was inhibited in the SEPs. 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 (2009) did. Therefore, this study applied tDCS to the M1 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.

Methods

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: 27, female: 23) and they were equally

Table 1. Demographic and general characteristics of the subjects (N=50)

	Stimulation group	Sham group	p-value
Gender (male/female)	10/15	17/8	
Age (year)	22.5±3.3[a]	21.9±1.9	.48
Height (㎝)	168.4±7.6	170.6±7.1	.27
Weight (㎏)	65.1±13.0	63.5±10.3	.60
NCS[b]			
Amplitude (㎷)	36.3±14.8	34.3±10.3	.54
Latency (㎳)	2.2±.2	2.2±.2	.83

[a]mean±standard deviation, [b]nerve conduction study.

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and randomly assigned to either a tDCS group or a sham tDCS group. Demographic data are shown in Table 1. Sufficient explanation was given to them and a written consent was obtained from them.

Electroneurography

All the subjects received electroneurography (Viking IV, Nicolet Co., Kennewick, 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 ℃ (skin temperature: 30 to 32 ℃), according to the method presented by Liverson and Ma (Nische and Paulus, 2001). Amplitudes and latencies of the sensory nerves were recorded.

Current perception threshold (CPT) test

CPT values of all subjects were calculated prior to the application of tDCS. The CPT test was conducted with a Neurometer® (Neurotron Inc., 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 ㎐, 250 ㎐, 5 ㎐ was applied to the subjects with an intensity of stimulation starting from .001 ㎃, until the subjects felt the electrical current for the first time. The stimulation intensity ranged from .001 ㎃ to 9.99 ㎃. When the subjects felt the electrical current, the stimulation was turned off. The intensity was then lowered to 100 ㎂, another stimulation was given, and the threshold values were checked. Stimulation was given again within an error margin of 20 ㎂ 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.

Transcranial direct current stimulation (tDCS)

The tDCS device, Phoresor® II Auto (PM850, IOMED®, Utah, USA) was used. The size of the two sponge electrodes attached to the scalp was 25 ㎠ (5 ㎝×5 ㎝) and their current density was .08 ㎃/㎠. The electrodes were soaked with .9% physiological saline and attached to the subjects as tightly as possible, but to an extent at which the subjects did

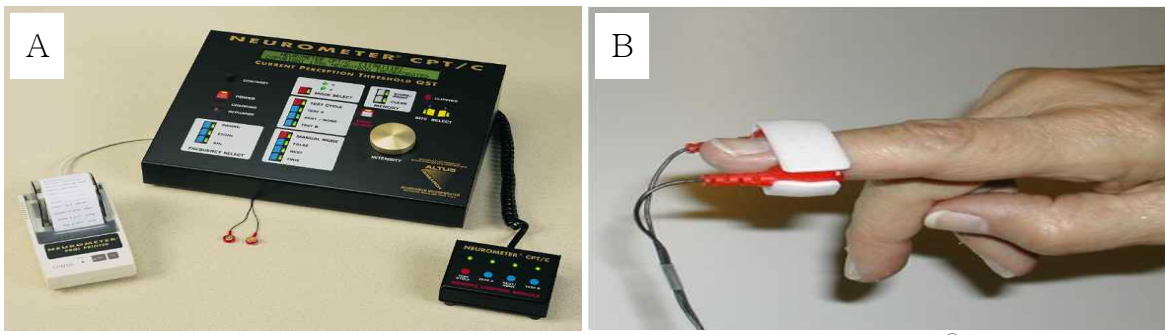

Figure 1. A: Method of current perception threshold test, B: A Neurometer® current perception threshold (CPT)/C was used to measure CPT values at frequencies of 2000, 250, and 5 ㎐ in the right finger to assess the tactile sense, fast pain, and slow pain, respectively.

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Figure 2. The equipment for the transcranial direct current stimulation and the stimulation targets (C3: central 3).

not feel discomfort. Following the International 10-20 system, the anodal electrode was attached to central 3 of the M1 and the cathodal electrode was attached to the upper part of the opposite orbital region of the M1 (Figure 2). In the anodal tDCS group, current intensity and stimulation time were set at 1 ㎃ and 15 minutes, respectively. In the sham tDCS group, the electrodes were attached to the M1 in the same way as for the tDCS group. After giving 1 ㎃ 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. (Gandiga et al, 2006).

Statistical analysis

In this study, statistical analysis was conducted with SPSS ver. 19.0 (SPSS, Inc., Chicago, IL, USA) and as a normality test the Kolmogorov-Smirov /Shapiro-Wilk test was carried out. A paired t-test was performed to compare the M1 between, prior to, and after the intervention in the tDCS group and the sham tDCS group. A statistical significance level was set at $p<.05$.

Results

Comparison of CPT values of the M1 between tDCS and sham tDCS groups

In the test to measure CPT values of the M1 in the tDCS group, the values of the distal part of the distal interphalangeal joint of the second finger statistically increased in all of 2000 ㎐, 250 ㎐, and 5 ㎐ ($p<.05$). However, the values of the sham tDCS group decreased in all of 2000 ㎐, 250 ㎐, and 5 ㎐, and were not statistically significant (Table 2).

Discussion

This study applied tDCS to the M1 of the cerebral cortex of healthy adult males and females, measured changes in their peripheral sensory nerves, and clarified the effects of tDCS on the sensory nerves,

Table 2. Comparison of pre-test and post-test CPT values in the tDCS and sham tDCS groups (N=50)

	Stimulation group			Sham group		
	2000 ㎐	250 ㎐	5 ㎐	2000 ㎐	250 ㎐	5 ㎐
Pre	261.20±84.32[a]	109.10±51.75	142.60±56.00	315.50±62.38	130.40±65.67	189.40±123.03
Post	310.60±91.96	175.50±78.99	207.50±94.49	299.50±53.59	122.40±65.13	126.70±54.52
p value	.000*	.002*	.008*	.285	.552	.062

[a]mean±standard deviation, *$p<.05$.

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thereby providing supportive materials for its clinical application. Regarding the effects of tDCS on the M1, the values increased with statistical significance in all of 2000 ㎐, 250 ㎐, and 5 ㎐, which means that the overall threshold values of nerve fibers such as Aβ, Aδ, and C, in other words, tactile sense, pressure sense, fast pain, slow pain, cold sense, and warm sense, all increased. Boggio et al (2008) applied anodal tDCS with 2 ㎃ current to the M1, DLPFC, and occipital cortex, and to sham tDCS for five minutes, and measured peripheral electrical stimulation. The result was a rise in the perception and pain thresholds of the M1, which is the result of controlling the activities of the thalamus and the brainstem nuclei, the most convincing mechanism of pain control, and is explained as stimulation to the M1 area that provides inhibitory control of the descending pathway to the spinal cord (Fregni and Pascual-Leone, 2007). Although differing intensities of stimulation were applied to the same area for a different time period in this study, a similar result with an increase in the thresholds of nerve fibers was obtained. This is considered to show the effects of stimulation under the, widely used tDCS application method, where current intensity is 1 to 2 ㎃, electrode size is 25 to 35 ㎠, and stimulation time is 20 to 30 minutes. Previous research also reported that sensory change in the M1 area was closely related to pain control, and that stimulation to the area led to pain alleviation and improvement in sensory differentiation ability (Drouot et al, 2002). In the present study, changes in such sensory functions were quantitatively analyzed by a neurometer, and CPT values increased after the application of tDCS to the M1 area. In healthy persons, not patients with pain, over-response by the thalamus and the brainstem nuclei does not occur, and therefore a strengthened inhibitory connection may result in a rise in CPT values. This was verified in other studies that examined sensory changes by a single transcranial magnetic stimulation, another non-invasive brain stimulation technique (Cohen et al, 1991; McKay et al, 2003; Morita et al, 1998). Lee (2007) reported that 10 ㎐ rapid TMS to the M1 area significantly raised current perception of 2000 ㎐, 250 ㎐, and 5 ㎐ and the pain tolerance threshold, and Kodama et al (2009) noted that low-frequency rTMS to the M1 area increased the sensory threshold. According to the CPT test results from the present study, there was an increase in the threshold of Aβ nerve fibers mediating tactile sense, vibration, and pressure, Aδ nerve fibers mediating pain induced by cold perception and cold sense, and C nerve fibers mediating pain induced by warm perception and warm heat. In a study of temperature perception and the pain threshold by rTMS, Satow et al (2003) reported that standard somatosensory-evoked potentials, related to the tactile threshold increased after application of .9 ㎐ rTMS. Oliviero et al (2005) and Summers et al (2004) observed significant changes in the cold pain threshold through a temperature and sensory threshold test. Tamura et al (2004) observed inhibition of the warm and heat pain thresholds and aggravation of cold pain in relation to laser evoked-potentials. The results of a study by Kodama et al (2009) were consistent with the present study's results regarding tactile and pain perception thresholds. Their study concerned a different non-invasive stimulation technique, but verified that sensory changes were closely associated with pain control. A diversity of treatment choices are considered possible for different types of chronic pain. This study examined changes in each sensory nerve fiber through a CPT test that had not been investigated in previous research, providing grounds to clarify the function control mechanism of tDCS stimulation and its effects. 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 M1 decreased. In previous studies, the sham tDCS group did not experience any change with no excitability of the cerebral cortex or decrease in the

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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 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.

tDCS has been tested in thousands of subjects world wide with no evidence of toxic effects to date. Poreisz et al (2007) reviewed adverse effects in 77 healthy subjects and 25 patients who underwent a total of 567, 1 ㎃ stimulation sessions. Results show the most common effects were mild tingling sensations (75%), light itching sensation (30%), moderate fatigue (35%), and headache (11.8%); and most of these effects did not differ from those of placebo stimulation.

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.

Conclusion

This study applied tDCS to the M1, 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 all Aβ, Aδ, and C nerve fibers of the M1 increased statistically significantly in the tDCS group. Although CPT values in the sham tDCS group decreased in the M1, 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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