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A transcranial direct current stimulation over the sensorimotor cortex modulates the itch sensation induced by histamine

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HIGHLIGHTS

- The effects of tDCS for itch relief were tested in a double-blind study.
- A bi-hemispheric tDCS over the sensorimotor cortex decreased subjective itch ratings.
- A tDCS intervention may be useful in the treatment of itching.

ABSTRACT

Objective: Itching can be suppressed by scratching. However, scratching may aggravate itch symptoms by damaging the skin. Therefore, identifying an alternative approach to suppress itching is of clinical importance. The aim of the present study was to determine whether a transcranial direct current stimulation (tDCS) was useful for itch relief.
Methods: The present study was performed on a double-blind, Sham-controlled, and cross-over experimental design. A histamine-induced itch was evoked on the left dorsal forearms of healthy participants, who were asked to report the subjective sensation of itching every 30 s for 23 min. tDCS was applied over the sensorimotor cortex (SMC) according to a bi-hemispheric stimulation protocol during the itch stimuli; one electrode was placed over the right SMC, while the other was placed over the left SMC. The peak and lasting sensations of itching were compared between R-A/L-C (anodal electrode placed over the right and cathodal electrode over the left), L-A/R-C (anodal electrode placed over the left and cathodal electrode over the right), and Sham interventions.
Results: The peak and lasting itch sensation were significantly suppressed during the R-A/L-C intervention than during the Sham intervention. On the other hand, the L-A/R-C intervention suppressed the peak itch sensation, but the effects did not last for more than a few minutes.
Conclusions: These results suggest that a bi-hemispheric tDCS intervention, especially when the anodal electrode was placed over the SMC of the contralateral side, was a potentially useful method for relieving lasting itch sensations.
Significance: The present study demonstrated that a tDCS intervention may be an alternative approach for suppressing unpleasant itch sensations in healthy participants. Since tDCS has some advantages, namely, its easy application and safety in a clinical setting, it may become a useful method for the treatment of itching.

1. Introduction

An itch is an unpleasant sensation that is accompanied by the desire to scratch, which is the easiest way to suppress this

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sensation (Davidson et al., 2009; Vierow et al., 2009; Mochizuki et al., 2014). However, it often causes skin damage and exacerbates the itch. Therefore, scratching represents a significant problem in patients with chronic itch sensations such as atopic dermatitis. Thus, other approaches for the relief of itching need to be identified.

Although an itch is a distinct sensation from pain, they share several features. Itch sensations are transmitted to the brain through C-fibers (Schmelz et al., 1997) and the spinothalamic tract (Andrew and Craig, 2001). The common brain regions activated by itch and pain stimuli include the insula, cingulate cortex, prefrontal cortex, inferior parietal cortex, pre-/supplementary motor cortex, somatosensory cortex, and basal ganglia (Drzezga et al., 2001; Mochizuki et al., 2007). Furthermore, some endogenous inhibitory mechanisms have also been detected in both processes. A previous study suggested that the periaqueductal gray matter in the midbrain was related to the modulation of itch, which is known to be a component of the pain modulation system (Mochizuki et al., 2003). Another study showed that strong stress-induced antinociception attenuated itch-related scratching in rats as well as nociceptive behaviors (Spradley et al., 2012).

A top-down approach by stimulating the primary somatosensory cortex (SI) or primary motor cortex (MI) has recently been investigated for the treatment of pain. Non-invasive brain stimulation techniques using a repetitive transcranial magnetic stimulation, theta burst stimulation, or transcranial direct current stimulation (tDCS) have been applied as useful options (Song et al., 2011; Mylius et al., 2012; Vaseghi et al., 2014). The intervention of tDCS has some advantages over other brain stimulation techniques because the device is portable, inexpensive, easy to apply, and safe in the setting of clinical practice (Poreisz et al., 2007; Tanaka and Watanabe, 2009). Previous studies demonstrated that tDCS interventions modulated experimentally-induced pain sensations in healthy subjects (Antal et al., 2008; Boggio et al., 2008; Terney et al., 2008; Csifcsak et al., 2009; Hansen et al., 2011; Reidler et al., 2012). One possible mechanism is that widespread changes in pain-related subcortical and cortical brain regions; however, this is still being debated because some studies failed to find positive effects (Jürgens et al., 2012; Ihle et al., 2014). The effects of the repeated application of tDCS to suppress various types of chronic pain such as fibromyalgia (Fregni et al., 2006b; Valle et al., 2009), spinal cord injury (Fregni et al., 2006a), multiple sclerosis (Mori et al., 2010), and migraine (Dasilva et al., 2012) have been investigated in clinical studies.

On the other hand, only one study has been reported for itch relief. This study examined the effects of a sustained tDCS intervention on neuropathic pain and itch sensations, and found that the tDCS intervention reduced the itch sensation (Knotkova et al., 2013). However, this investigation was only performed on a single patient. Thus, a quantitative evaluation with more subjects needs to be performed in order to verify whether tDCS has positive effects on itch relief. This issue was investigated in the present study.

The SI area is considered to play an important role in the intensity coding of itch sensations (Drzezga et al., 2001), and was previously shown to be activated with contralateral hemisphere predominance (Darsow et al., 2000; Ishiuji et al., 2009; Mochizuki et al., 2009). Thus, we targeted the contralateral SI area to modulate itch sensations. Recent tDCS studies that targeted SI or MI reported that a bi-hemispheric intervention represented a more powerful strategy for modulating sensory or motor functions than a uni-hemispheric stimulation (Vines et al., 2008; Fujimoto et al., 2014; Koyama et al., 2015). These findings suggested that the bi-hemispheric intervention yielded the combined effects of increased excitability from anodal tDCS and decreased interhemispheric inhibition from cathodal tDCS over the ipsilateral side. Therefore, we here in addressed the efficacy of bi-hemispheric tDCS interventions over the SI for itch sensations in healthy subjects using a double-blind, Sham-controlled, and cross-over experimental design.

2. Methods

2.1. Participants

Fourteen healthy volunteers (2 females and 12 males, mean age: 30.9 ± 6.9 years, 13 right-handed and 1 left-handed) participated in the present study. Before measurements were taken, we confirmed that participants did not use anti-histaminic or anti-inflammatory drugs or have immunological and dermatological diseases. This study was approved by the Ethics Committee at the National Institute for Physiological Sciences (NIPS). Written informed consent was obtained from each participant in every session. This study was performed in compliance with the relevant laws and guidelines of NIPS.

2.2. Itch stimuli

An electrode (anode: diameter, 20 mm) infiltrated with histamine gel and a reference electrode (cathode) were attached to the participants' left ventral forearms (Fig. 1A). The histamine gel consisted of histamine (Sigma, St. Louis, MO, U.S.A.) dissolved in saline with 2.5% methylcellulose (Kanto Chemical, Tokyo, Japan). The concentration of histamine was 0.5% in the present study. An electrical current (0.5 mA) was applied to the electrodes for 30 s using an electrical stimulator (SEN-7203, Nihon Koden Inc., Tokyo, Japan) in order to allow histamine to pass into the skin.

The subjective sensation of itching was evaluated using a numerical scale, which is widely used in tDCS studies of pain (Antal et al., 2008; Terney et al., 2008; Csifcsak et al., 2009; Hansen et al., 2011). Participants reported their subjective sensation of itching by typing a keyboard (buttons 1 to 9) with the right hand every 30 s for a total of 23 min (Fig. 1B). A score of 1 indicated no itch, while a score of 9 indicated an unbearable itch (a revised numerical rating scale; rNRS). Because most participants were right-handed, we chose the left hand to induce itch and asked the participants to type a keyboard with the right hand.

2.3. tDCS

The present study was performed according to a bi-hemispheric tDCS protocol; one electrode was placed over the SI of the contralateral side to the stimulated hand and the other was placed over the ipsilateral side. tDCS was delivered using a DC Stimulator Plus (NeuroConn, Ilmenau, Germany) with a direct current through two sponge surface electrodes. Relatively large electrodes (each with a surface area of 25 cm^2) were used to maintain low impedances (Norris et al., 2010).

Before the experiments, T1-weighted anatomical MR images were obtained in all participants with a 3-T MR imager (MAGNETOM Verio; Siemens, Erlangen, Germany). We then localized bilateral SI using a frameless stereotaxic navigation system (Brainsight 2; Rogue Research Inc., Montreal, Canada) and the centers of the stimulation electrodes were placed over the SI for each participant (Fujimoto et al., 2014). In order to localize the SI area, we first detected the "hand knob" MI region by referring to a previous study (Mylius et al., 2013), then identified SI area 2 cm posterior to the MI. However, it was hard to stimulate by dividing SI and MI because of the large electrodes. Therefore, we referred to the stimulated area as the 'sensorimotor' cortex (SMC), as described in a previous study (Matsunaga et al., 2004).

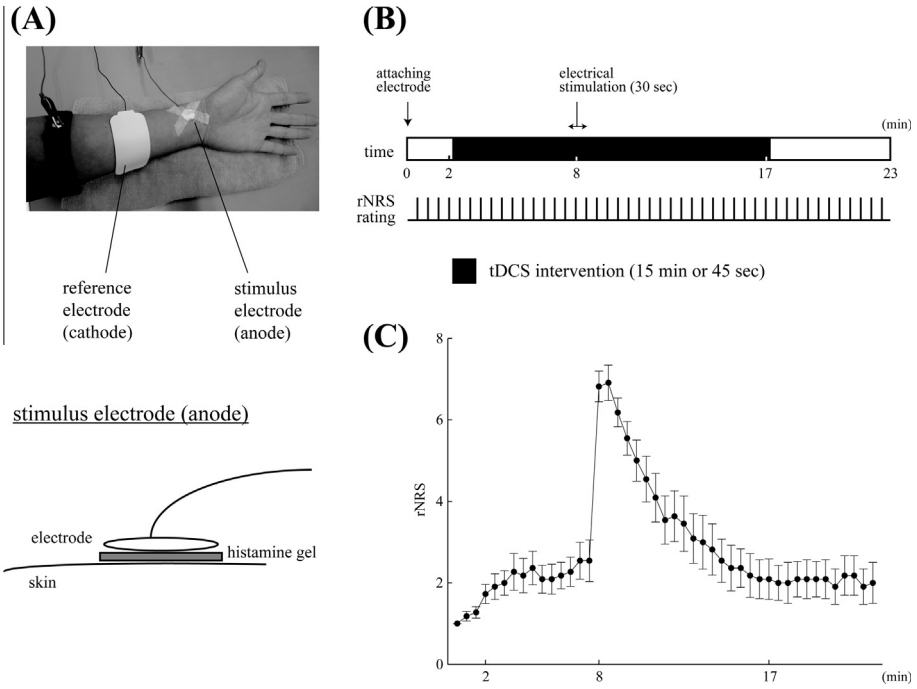

Fig. 1. Experimental design. (A) Methods for the histamine-induced itch stimulation. Stimulus electrodes were attached to the left forearm infiltrated with histamine gel. (B) Time course of the experiment. Participants reported rNRS scores every 30 s for a total of 23 min. Histamine was passed into the skin by an electrical stimulation 7.5 min after attaching the electrodes. The R-A/L-C and L-A/R-C interventions were applied for 15 min, whereas the Sham was only applied for 45 s. The tDCS intervention was applied 2 min after attaching the electrodes. (C) Time-dependent changes in the subjective itch sensation (rNRS scores) for the Sham condition. Data represent the mean ± standard error (SE). Subjective itch sensations peaked immediately after the electrical stimulation, and the score subsequently decreased toward the baseline.

In each session, the intensity of the direct current stimulation was 1.0 mA, and was applied for 15 min (including the initial and last 15 s, which gradually increased from zero and decreased toward zero). The same procedure was used in the Sham stimulation, but was only applied for 45 s (including the initial and last 15 s). These parameters were in line with previous studies on experimentally-induced pain modulation (Antal et al., 2008; Terney et al., 2008; Jürgens et al., 2012; Ihle et al., 2014).

2.4. Task procedures

The present study was performed on a Sham-controlled and cross-over experimental design. Each volunteer participated in three experimental sessions with distinct tDCS conditions; (1) R-A/L-C; the anodal electrode was placed over the right SMC and the cathodal electrode over the left SMC, (2) L-A/R-C; the anodal electrode was placed over the left SMC and the cathodal electrode over the right SMC, and (3) Sham. The order of the sessions was counter-balanced across the participants, and each experimental session was performed on a different day separated by at least one week. We adopted a double-blind procedure to guard against experimental biases. Two researchers performed the experiment; one interacted with the participants and administered itch stimuli, whereas the other only administered the tDCS stimulation. Neither the participants nor the researcher interacting with participants were aware of the tDCS conditions throughout the experiments.

Participants sat on a comfortable chair, and placed their left arm on a comfortable arm rest in an air-conditioned room. They were instructed not to move or scratch their left arm during the sessions. The tDCS intervention and electrical stimulus for the histamine-induced itch were applied 2 min and 7.5 min after attaching the electrode, respectively.

After the measurements, a questionnaire was provided for each tDCS intervention on the scalp. Participants filled out the level of the pain sensation (1 = no pain, 4 = strongest pain), itch sensation (1 = no itch, 4 = strongest itch), tingling sensation (1 = no tingling, 4 = strongest tingling), discomfort (1 = no discomfort, 4 = strongest comfort), fatigue (1 = no fatigue, 4 = highest level of fatigue), and attention (1 = no distraction of attention, 4 = highest distraction of attention) due to the tDCS intervention using a four-point scale (Poreisz et al., 2007; Fujimoto et al., 2014).

2.5. Analysis

We analyzed the peak intensity of and decrements in the itch sensation. Although most participants perceived an intense itch sensation after the electrical stimulus for the histamine-induced itch, the perceived itch sensation of 3 participants was too weak to evaluate the effects of tDCS on itch sensations. Therefore, we excluded these 3 participants from further analyses. Accordingly, data from 11 participants (2 females and 9 males, mean age: 31.7 ± 7.6 years) were analyzed.

The peak intensity of the itch sensation was compared using a one-way repeated ANOVA among the three tDCS interventions. The intensity of an itch sensation was previously shown to markedly decrease 5–6 min after the application of histamine (Leknes et al., 2007). We considered it difficult to evaluate the effects of tDCS if the itch sensation was very weak. Therefore, decrements in the intensity of the itch were compared with time-dependent changes for 6 min every 2 min from the peak intensity of the itch for each participant (lasting period). A two-way repeated ANOVA (3 time points × 3 tDCS interventions) was adopted for comparisons. In both analyses, post hoc tests with a Bonferroni correction were applied where appropriate to compare differences in the tDCS condition. The questionnaire scales were analyzed using the Friedman rank test. The level of significance was set at $p < 0.05$ for ANOVA and the Friedman rank test, and $p < 0.017$ for the post hoc tests. All statistical analyses were carried out using the SPSS statistical package (version 20, IBM, New York, U.S.A.).

3. Results

As shown in Fig. 1C, the itch sensation peaked immediately after the electrical stimulus for the histamine-induced itch and decreased over time. The means ± SD of rNRS scores before the tDCS intervention were 1.2 ± 0.2 for R-A/L-C, 1.2 ± 0.3 for L-A/R-C, and 1.3 ± 0.4 for Sham. No significant differences were observed before the tDCS intervention ($F(2, 20) = 1.36$, $p = 0.28$, partial $\eta^2 = 0.12$).

3.1. Differences in subjective itch sensations

Fig. 2 shows the peak intensity of rNRS for each tDCS intervention. The itch sensation reached a peak within 1.5 min of the electrical stimulus for the histamine-induced itch. The scores (means ± SD) were 6.7 ± 1.2 for R-A/L-C, 6.9 ± 1.0 for L-A/R-C, and 7.5 ± 0.9 for Sham. A significant difference was noted among the sessions ($F(2, 20) = 4.38$, $p < 0.05$). Post-hoc tests revealed that the score of Sham was significantly higher than those of the R-A/L-C ($p = 0.011$) and L-A/R-C ($p = 0.011$).

Itch sensations gradually decreased after the electrical stimulus, and the extent of the decrement was different among the sessions (Fig. 3). A two-way repeated ANOVA (3 time points × 3 tDCS sessions) revealed a significant difference in scores among the time points ($F(2, 20) = 33.02$, $p < 0.001$) and tDCS sessions ($F(2, 20) = 3.63$, $p = 0.045$). No significant interaction was found between the two factors ($F(4, 40) = 0.171$, $p = 0.952$). Post-hoc tests revealed that the score of the R-A/L-C intervention was significantly lower than that of Sham ($p = 0.014$) 2 min after the peak intensity of itch was felt, whereas no significant differences were observed between the L-A/R-C and Sham interventions (Table 1).

3.2. Questionnaire scores

No significant differences were note in any of the questionnaire scores among the three tDCS sessions (Table 2). This result indicated that the subjective state to the tDCS intervention on the scalp did not influence the subjective histamine-induced itch sensation on the forearm.

4. Discussion

The present study demonstrated histamine-induced itch modulation during bi-hemispheric tDCS interventions over the SMC using a double-blind, Sham-controlled, and cross-over design. We revealed that the R-A/L-C intervention (anodal electrode placed over the SMC of the contralateral side to the stimulated hand and cathodal electrode placed over that of the ipsilateral one) significantly decreased the peak and lasting subjective itch sensation, whereas the inhibitory effects of the reverse layout (the L-A/R-C intervention) did not last for more than a few minutes.

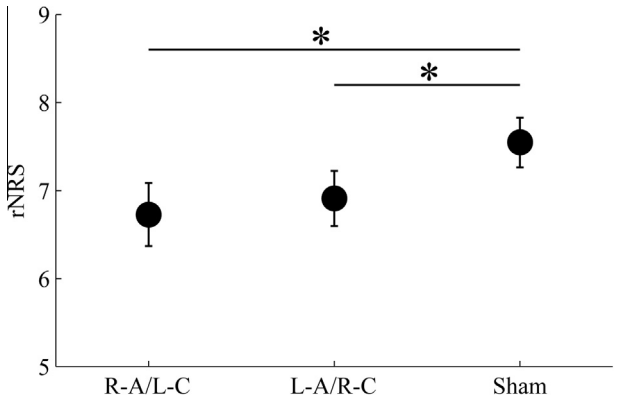

Fig. 2. Comparison of peak rNRS scores among the three tDCS interventions. Data represent the mean ± SE. $^{*}p < 0.05$.

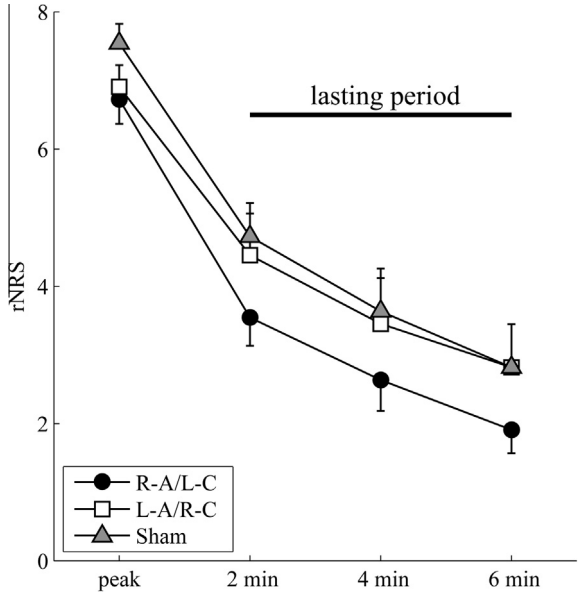

Fig. 3. Time-dependent changes in itch sensations with 2 min intervals from the peak intensity. Data represent the mean ± SE.

Table 1
p-Values with the post hoc test at each time phase (lasting period).

	2 min	4 min	6 min
R-A/L-C vs L-A/R-C	.211	.121	.033
R-A/L-C vs Sham	.014	.049	.074
L-A/R-C vs Sham	.602	.703	1

Table 2
Questionnaire scores after each tDCS intervention.

	rNRS score		
	R-Anodal	R-Cathodal	Sham
Pain	1.0 ± 0	1.1 ± 0.3	1.0 ± 0
Itch	1.1 ± 0.3	1.1 ± 0.3	1.0 ± 0
Tingling	1.4 ± 0.5	1.4 ± 0.5	1.1 ± 0.3
Discomfort	1.0 ± 0	1.0 ± 0	1.0 ± 0
Fatigue	1.0 ± 0	1.0 ± 0	1.1 ± 0.3
Attention	1.0 ± 0	1.0 ± 0	1.1 ± 0.3

4.1. Similarities and differences in itch and pain modulation

To the best of our knowledge, itch modulation by the application of tDCS has not yet been investigated, except for a case report that observed a positive effect on itch relief (Knotkova et al., 2013). Thus, a quantitative evaluation of this effect with more subjects was conducted in the present study. The results obtained in the present study supported the finding that itch sensations were relieved by a tDCS intervention over the SMC.

Previous studies examined the inhibitory effects of a uni-hemispheric tDCS intervention over the contralateral SI or MI on the perception of experimentally-induced somatic sensations. Although that electrode (anodal or cathodal) that had inhibitory effects differed between studies, most reported that the cathodal intervention was advantageous for increments in somatic

thresholds (Bachmann et al., 2010; Grundmann et al., 2011) and decrements in innocuous and painful somatosensory-evoked potentials (Dieckhöfer et al., 2006; Antal et al., 2008; Terney et al., 2008; Csifcsak et al., 2009; Hansen et al., 2011). On the other hand, the present study revealed antipruritic effects on the lasting itch sensation when the anodal tDCS over the contralateral SMC was applied. We attributed differences in the methodologies employed to the polar difference. The previous studies that we referred to above evaluated how somatic sensations were modulated after the end of the tDCS intervention, whereas the present itch study assessed this during the intervention. The impact of tDCS on physiological activity in the brain has been shown to differ between during and after a tDCS intervention (Stagg and Nitsche, 2011). The membrane resting potential of the stimulated area was previously shown to be changed during a tDCS intervention (Nitsche et al., 2003, 2005), whereas synaptic transmission was modulated after the intervention (Liebetanz et al., 2002). These differences suggest that the effects of a tDCS intervention on somatic sensations may differ between during and after the intervention.

A difference in the types of peripheral nerve fibers may also explain the polar difference. In previous studies, the somatic sensations used were painful thermal sensations mediated by A delta- and C-fibers (Kenton et al., 1980; Bromm et al., 1984), innocuous thermal sensations mediated by A delta-(cold) or C-fibers (warm) (Fowler et al., 1988), painful mechanical sensations mediated by A delta-fibers (Magerl et al., 2001), and innocuous mechanical sensations mediated by A beta-fibers (Torebjörk et al., 1987). In contrast, histamine-induced itch sensation mediated by different types of peripheral fibers such as C-fibers, which are insensitive to mechanical and heat stimuli (CMiHi) (Schmelz et al., 1997). Tolerance time in the cold pressor test (i.e., the immersion of a participant's hand in cold water) was found to increase during anodal stimulation over the MI (Zandieh et al., 2013), and was mainly attributed to the activity of C-fibers (Fruhstorfer and Lindblom, 1983). Some types of C-fibers such as CMiHi and C-fibers associated with cold deep pain may be more sensitive to an anodal tDCS intervention than other types of peripheral nerve fibers.

4.2. Possible central mechanisms of the itch modulation by the tDCS intervention over the bilateral SMC

A previous positron emission tomography study investigated how a tDCS intervention over the MI altered regional neuronal activity in the human brain (Lang et al., 2005). They found that a uni-hemispheric anodal tDCS modulated widespread cortical and subcortical regions including the inferior parietal cortex, cingulate cortex, and thalamus via cortico-cortical and cortico-subcortical connections. These regions have been associated with the cognitive aspects of pain (Lorenz et al., 2003), and also play important roles in the processing of itch sensations (Mochizuki and Kakigi, 2015). Therefore, the anodal tDCS intervention over the SMC may have suppressed itch sensations through the indirect effects of neural networks. However, we were unable to clarify which brain regions correlated with the relief of itch sensations in the present study.

Since the present study followed a bi-hemispheric tDCS protocol, we need to consider the combined effects that increased the excitability of one hemisphere, while decreasing that of the other. Inter-hemispheric connections are present between the bilateral SI; therefore, the decrement observed in the excitability of the left SMC may also have affected the increment of the excitability of the right SMC through a reduction in the inter-hemispheric inhibition under the R-A/L-C condition. We were unable to establish whether the uni-hemispheric intervention was sufficient for itch relief. However, a previous study reported that a bi-hemispheric tDCS over the SI facilitated greater improvements for performance in a tactile discrimination skill than a uni-hemispheric tDCS (Fujimoto et al., 2014). Another study reported that a bi-hemispheric tDCS over M1 affected the enhanced consolidation of ballistic thumb movements, whereas they did not observe any significant performance improvement with a uni-hemispheric tDCS over that with a Sham stimulation (Koyama et al., 2015). Based on these findings, we suggested that the bi-hemispheric intervention, increasing the excitability of one hemisphere while decreasing that of the other, was more effective for itch modulation than uni-hemispheric intervention.

4.3. Limitations

The observed effect-size in the present study was not large (partial $\eta^2 = 0.27$) and raised some questions about the clinical significance of the observed effect. To the best of our knowledge, the analgesic effects of tDCS on experimentally-induced pain were significant, whereas the effect sizes were not large (e.g. partial η^2 was 0.28 in the Antal et al. study (2008) and 0.13 in the Boggio et al. study (2008), according to our calculations), which was consistent with our results. On the other hand, clinical studies showed significant analgesic effects on chronic pain (e.g. partial η^2 was 0.37 in Fregni et al. study (2006a) and 0.50 in Mori et al. study (2010), according to our calculations). These studies reported approximately 50% reductions in chronic pain from several days to several weeks. Unlike other studies on experimentally-induced pain, clinical studies employed repeated application (5–10 days) of tDCS with higher intensity currents (2.0 mA) (Fregni et al., 2006a,b; Valle et al., 2009; Mori et al., 2010; Dasilva et al., 2012), which may have been important for obtaining clinically meaningful antipruritic effects. In future studies, we need to verify whether it is possible to obtain clinically meaningful antipruritic effects when tDCS is repeatedly applied, as demonstrated by previous studies using chronic pain patients.

5. Conclusions

We confirmed the antipruritic effects of experimentally-induced itch sensations in healthy participants. By combining the results obtained in the present study with the findings of a previous case report, we suggest that a SMC stimulation using tDCS is useful for the treatment of itching. Further studies are needed to explore more effective stimulus conditions for this method for future clinical applications.

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Conflict of interest: There is no conflict of interest associated with the submission of this manuscript.

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