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Review article

Adverse events of tDCS and tACS: A review

Hideyuki Matsumoto [a,*], Yoshikazu Ugawa [b,c,1]

[a] Department of Neurology, Japanese Red Cross Medical Center, Japan
[b] Department of Neurology, School of Medicine, Fukushima Medical University, Japan
[c] Fukushima Global Medical Science Center, Advanced Clinical Research Center, Fukushima Medical University, Fukushima, Japan

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ABSTRACT

Transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS) have been applied to many research issues because these stimulation techniques can modulate neural activity in the human brain painlessly and non-invasively with weak electrical currents. However, there are no formal safety guidelines for the selection of stimulus parameters in either tDCS or tACS. As a means of gathering the information that is needed to produce safety guidelines, in this article, we summarize the adverse events of tDCS and tACS. In both stimulation techniques, most adverse effects are mild and disappear soon after stimulation. Nevertheless, several papers have reported that, in tDCS, some adverse events persist even after stimulation. The persistent events consist of skin lesions similar to burns, which can arise even in healthy subjects, and mania or hypomania in patients with depression. Recently, one paper reported a pediatric patient presenting with seizure after tDCS, although the causal relationship between stimulation and seizure is not clear. As this seizure is the only serious adverse events yet reported in connection with tDCS, tDCS is considered safe. In tACS, meanwhile, no persistent adverse events have been reported, but considerably fewer reports are available on the safety of tACS than on the safety of tDCS. Therefore, to establish the safety of tDCS and tACS, we need to scan the literature continuously for information on the adverse events of both stimulation techniques. Further safety investigations are also required.

Contents

1. Introduction

Since the first reports of transcranial direct current stimulation (tDCS) by Priori et al. (1998) and Nitsche and Paulus (2000, 2001), tDCS has been applied to many research issues because it can modulate the neural networks in the human brain painlessly and

Abbreviations: EEG, electroencephalography; MRI, magnetic resonance imaging; NSE, neuron specific enolase; rTMS, repetitive transcranial magnetic stimulation; tACS, transcranial alternating current stimulation; tDCS, transcranial direct current stimulation.

* Corresponding author at: Department of Neurology, Japanese Red Cross Medical Center, 4-1-22 Hiroo, Shibuya-ku, Tokyo 150-8935, Japan.
E-mail addresses: hideyukimatsumoto.jp@gmail.com (H. Matsumoto), ugawa-tky@umin.net (Y. Ugawa).
[1] Department of Neurology, Faculty of Medicine, Fukushima Medical University, 1 Hikarigaoka, Fukushima 960-1295, Japan.

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non-invasively (Priori et al., 1998; Nitsche and Paulus, 2000, 2001). In other words, tDCS can induce neural plasticity (Ugawa, 2012). Most of its adverse effects are mild and disappear soon after stimulation, but several papers have reported that some adverse effects, most commonly skin problems, can persist even after stimulation. Recently, since the invention of transcranial alternating current stimulation (tACS) by Antal et al. (2008), tACS has also been applied in research for the modulation of neural activity through the entrainment on brain oscillations (Antal et al., 2008; Antal and Herrmann, 2016). As in tDCS, the adverse effects of tACS are mild and disappear just after stimulation. Yet there have been far fewer papers on safety issues or adverse events of tACS as compared to tDCS. To date, there are no formal safety guidelines for the selection of stimulus parameters in either tDCS or tACS (Fertonani et al., 2015). Therefore, we aim to summarize the adverse events of tDCS and tACS in this review. At present, the safety and ethical issues of both stimulation techniques should be considered by each institution due to the lack of certainty about their risks. This review may provide some useful information for these considerations. In addition, this review is expected to be useful for the establishment of safety guidelines in the near future.

1.1. Adverse events of tDCS

Nitsche et al. (2003) performed tDCS in approximately 500 healthy subjects between 2000 and 2003. The stimulus electrode was placed over the primary motor cortex and the reference electrode over the contralateral supraorbital area. The stimulus electrode was 5 cm × 7 cm. Weak direct currents of 1 mA were administered for up to 20 min (current density was 0.029 mA/cm^2). Using this protocol, no serious adverse events such as seizure or psychotic symptoms were reported, apart from a slight tingling sensation under the electrode during the first seconds of stimulation or the sensation of a short light flash if the stimulation was switched on or off abruptly (Nitsche et al., 2003a,b). Similarly, Iyer et al. (2005) also reported no serious adverse events of tDCS. Electrical currents of 1 mA or 2 mA were administered for up to 20 min with the stimulus electrode over the prefrontal cortex and the reference electrode over the contralateral supraorbital area (current density was 0.04 or 0.08 mA/cm^2). Only transient redness under the stimulus electrode was observed in two out of 103 healthy subjects (Iyer et al., 2005). Poreisz et al. (2007) summarized the adverse events seen in 567 tDCS sessions in 102 subjects (77 healthy subjects and 25 patients with migraine, post-stroke, or tinnitus) obtained from a questionnaire. tDCS consisted of a 1 mA electrical current lasting between 9 and 15 min (current density was 0.029 mA/cm^2); the electrodes were placed over motor and non-motor cortical areas such as the occipital, temporal, and parietal areas. The adverse events were a mild tingling sensation (70.6%), moderate fatigue (35.3%), and a light itching sensation under the stimulus electrode (30.4%), which were observed even with sham tDCS. Additionally, the most common adverse events were skin problems, although the skin problems disappeared after tDCS. After tDCS, headache (11.8%), nausea (2.9%) and insomnia (0.98%) were reported (Poreisz et al., 2007). The incidence of remarkable adverse events such as headache was much lower after tDCS than after repetitive transcranial magnetic stimulation (rTMS) (11.8% in tDCS and 23% in rTMS) (Machii et al., 2006; Rossi et al., 2009; Matsumoto and Ugawa, 2011; Rossini et al., 2015). Liebetanz et al. (2009) estimated the tDCS threshold for producing brain lesions in rats to be 52,400 C/m^2, which is far higher than the common charge density in humans (e.g. 343–960 C/m^2 in the standard protocol: 1–2 mA × 20 min with 25–35 cm^2 large, wet sponge electrodes) (Liebetanz et al., 2009). The standard protocols have been widely used in healthy subjects as well as patients with neurological and psychological disorders (Fregni et al., 2006a,b; Webster et al., 2006; Bikson et al., 2008; Furubayashi et al., 2008; Arul-Anandam et al., 2009; Shirota et al., 2014; Matsumoto and Ugawa, 2016), and only transient skin problems under the electrodes have been reported (Wassermann and Grafman, 2005; Lagopoulos and Degabriele, 2008; Bikson et al., 2009; Dell'Osso et al., 2011; Ugawa et al., 2011). In addition, several reports supported the safety of tDCS by studying parameters such as neuron-specific enolase (NSE: a sensitive marker of neuronal damage) (Nitsche and Paulus, 2001; Nitsche et al., 2003c), magnetic resonance imaging (MRI) (Nitsche et al., 2004), electroencephalography (EEG), and neuropsychological tests (Iyer et al., 2005; Tadini et al., 2011).

Brunoni et al. (2011) retrospectively reviewed the adverse events of tDCS from 209 experiments (172 reports). The main adverse events were itching (active vs. sham tDCS group: 39.3% vs. 32.9%), tingling (22.2% vs. 18.3%), headache (14.8% vs. 16.2%), discomfort (10.4% vs. 13.4%), and burning sensation (8.7% vs. 10%), none of which were significantly more common in the active tDCS group than in the sham tDCS group (Brunoni et al., 2011a). Similarly, prior studies also suggested that there was no difference in adverse events between active and sham tDCS groups (Gandiga et al., 2006; Brunoni et al., 2011a; Tadini et al., 2011). On the other hand, Kessler et al. (2012) prospectively compared the adverse events between active and sham tDCS groups in a relatively large number of subjects (131 healthy subjects, 277 tDCS sessions with the standard protocol). The adverse events were tingling (76%), itching (68%), burning sensation (54%), and pain (25%), and although all of these were mild, they had statistically significantly higher incidences in the active tDCS group than in the sham tDCS group. The incidence of adverse events in the prospective study was higher than that in the retrospective study (Kessler et al., 2012). Palm et al. (2013) also reported skin redness only in active tDCS but not in sham tDCS (Palm et al., 2013). Persistent skin lesions were rare and were hardly ever observed even in patients with vitiligo (Shiozawa et al., 2013). On the other hand, repeated daily tDCS with a current density of about 0.06 mA/cm^2 (e.g. if the stimulus electrode is 25–35 cm^2, current is 1.5–2.1 mA as in the standard protocols) caused clinically significant skin irritation under the electrodes in some patients (Nitsche et al., 2008) though not in all studies (Richmond et al., 2013). Actually, as shown in Table 1, persistent skin lesions under the electrodes have been reported by several authors (Palm et al., 2008; Frank et al., 2010; Kasahara et al., 2011; Riedel et al., 2012; Rodríguez et al., 2014; Wang et al., 2015). Most cases were analogous to skin burn and tended to occur on the front side of the scalp (forehead or frontal cortical areas). In addition, small skin lesions could occur even when small electrical currents were used (1 mA/0.029 mA/cm^2) (Kasahara et al., 2011). Some authors have reported contact dermatitis induced by electrodes as a generic skin lesion (Riedel et al., 2012). Several causative factors for such skin lesions have been proposed, including electrode position (the front side of the scalp due to curvature and lack of hair), skin conditions, allergic predisposition, skin preparations, high skin impedances, high electrical currents, duration of stimulation, repeated sessions, small electrodes (high current density), electrode shape, dry electrodes, inadequate fixation of electrodes, non-uniform contact pressure of electrodes to skin, extensive skin heating, solution salinity of electrode sponges, sponge shape, and deterioration of the sponges (Dundas et al., 2007; Palm et al., 2008, 2014; Frank et al., 2010; Norris et al., 2010; Kasahara et al., 2011; McFadden et al., 2011; Ugawa et al., 2011; Riedel et al., 2012; Guleyupoglu et al., 2014; Rodríguez et al., 2014; Turi et al., 2014; Wang et al., 2015; Guarienti et al., 2015).

Particularly when higher electrical currents are employed, more attention should be paid to these factors. To reduce the incidence of tDCS-induced skin lesions, further investigations including these

Table 1
Persistent skin lesions induced by tDCS.

	Subjects/Patients	Polarity	Stimulus electrode position	Reference electrode position	Electrical currents	Adverse effects
Palm et al. (2008)	5 patients with depression	A	F3	Contralateral supraorbital	2 mA 0.057 mA/cm^2	Skin lesions under reference electrode
Frank et al. (2010)	3 patients with chronic tinnitus	C	F3	F4	1.5 mA 0.043 mA/cm^2	Skin lesions under stimulus electrode
Kasahara et al. (2011)	2 healthy subjects	A	premotor	mental protuberance	1 mA 0.029 mA/cm^2	Small skin lesions under stimulus electrode
Riedel et al. (2012)	1 healthy subject	C	posterior superior temporal sulcus	supraorbital	0.75 mA C: 0.083 mA/cm^2 A: 0.0075 mA/cm^2	Contact dermatitis under both electrodes
Rodríguez et al. (2014)	3 patients with neuropathic pain	A	C3 or C4	contralateral supraorbital	2 mA 0.057 mA/cm^2	Skin lesions under reference electrode
Wang et al. (2015)	1 healthy subject	A	F3	contralateral supraorbital	2 mA 0.057 mA/cm^2	Skin burn under reference electrode

tDCS: transcranial direct current stimulation, A: anode, C: cathode.

Table 2
Treatment-emergent mania or hypomania during tDCS.

	Patients	Polarity	Stimulus electrode position	Reference electrode position	Electrical currents	Adverse effects
Arul-Anandam et al. (2010)	1 patient with unipolar depression	A	F3	contralateral supraorbital	1 mA 0.029 mA/cm^2	Hypomania
Baccaro et al. (2010)	1 patient with unipolar depression	A	F3	F4	2 mA 0.06 mA/cm^2	Hypomania
Brunoni et al. (2011b)	1 patient with unipolar depression	A	F3	F4	2 mA 0.06 mA/cm^2	Mania
Gálvez et al. (2011)	1 patient with bipolar depression	A	F3	Contralateral arm	2 mA –	Hypomania
Brunoni et al. (2013)	6 patients with unipolar depression	A	F3	F4	2 mA 0.08 mA/cm^2	4 hypomania and 2 mania
Pereira Junior Bde et al. (2015)	1 patient with bipolar depression	A	F3	F4	2 mA 0.08 mA/cm^2	Hypomania

tDCS: transcranial direct current stimulation, A: anode, C: cathode.

factors are required. At this point in time, participants should at least be instructed to report any discomfort immediately.

We should also consider cognitive adverse events. In most cases, the only effects of tDCS on cognitive functions were transient improvements or impairments in performance (Nitsche et al., 2003d, Antal et al., 2004a,b, Iyer et al., 2005; Kuo et al., 2008; Tadini et al., 2011). Recently, however, as shown in Table 2, treatment-emergent mania and hypomania have been reported in unipolar and bipolar depression treatment trials (Arul-Anandam et al., 2010; Baccaro et al., 2010; Brunoni et al., 2011b, 2013; Gálvez et al., 2011; Pereira Junior Bde et al., 2015). Brunoni et al. (2013) reported six patients with treatment-emergent mania or hypomania induced by tDCS trials for major depressive disorder. The incidence of hypomania or mania was higher after tDCS than after rTMS (Xia et al., 2008; Rossi et al., 2009; Matsumoto and Ugawa, 2011; Brunoni et al., 2013). Currently, however, we cannot judge whether tDCS really induces the adverse cognitive effects in patients with unipolar and bipolar depression, because most of the patients received tDCS in combination with medications. Medications alone may induce hypomania or mania regardless of tDCS. Alternatively, hypomania or mania may be explained by the underlying disease. In contrast, tDCS may have adverse effects on cognition through a synergistic mechanism.

Future studies are needed to identify which tDCS parameters, such as electrical current (current density), electrode position, duration of stimulation, and number of stimulation sessions have the most influence on the incidence of emotional adverse events. Augmentation with antidepressants is one issue to be studied in connection with treatment-emergent mania or hypomania, and the combination of tDCS and pharmacotherapy should also be carefully investigated (Brunoni et al., 2011b, 2012).

Historically, the most serious adverse event was observed in the first study of tDCS. Lippold and Redfearn (1964) reported that one healthy subject presented with respiratory and motor paralysis with cramping of the hands accompanied by nausea during the stimulation. Respiration returned when the stimulation was stopped. Consciousness was preserved. The stimulus protocol consisted of 10 sessions each of 0.3 mA cathodal stimulation for 16 min with bifrontal stimulus electrodes and the reference electrode on the leg, although the patient received 10 times the intended amperage, probably 3 mA (Lippold and Redfearn, 1964; Redfearn et al., 1964; Nitsche et al., 2008). Since this report is so old that the tDCS stimulator and setting used in this case are now outdated, these adverse events should not be directly compared to those in the current standard protocols. Vandermeeren et al. (2010) investigated the effect of tDCS with an extracephalic reference electrode on cardio-respiratory and autonomic functions in 30 healthy subjects. Although the electrical currents were smaller (1 mA) than those in the previous papers (Lippold and Redfearn, 1964; Redfearn et al., 1964), tDCS with the extracephalic reference electrode had no adverse effects on cardio-respiratory and autonomic functions (Vandermeeren et al., 2010). Currently, however, electrical currents of 3 mA or higher should be avoided when using an extracephalic reference electrode.

Most laboratories use standard protocols in which serious adverse events are rare. In contrast, longer-lasting protocols are also available. In a personal observation attributed to Wassermann EM, tDCS for up to 50 min induced neither cognitive nor emotional disturbances in healthy subjects (Nitsche et al., 2008). Before relatively strong tDCS protocols can be applied for long periods, further safety investigations are required. tDCS has been applied to children (normal subjects and patients) as well as adults. Mattai

et al. (2011) investigated the tolerability of tDCS over 10 sessions in 13 patients with childhood-onset schizophrenia. tDCS was well tolerated without any serious adverse events (Mattai et al., 2011). Andrade et al. (2014) investigated the adverse events of tDCS over 10 sessions in 14 healthy children. Adverse events were acute mood changes (42.9%), irritability (35.7%), tingling (28.6%), and itching (28.6%) (Andrade et al., 2014). Krishnan et al. (2015) reviewed the tDCS reports of 198 child patients. The current intensity administered to these patients ranged from 0.03 to 2.0 mA, and the duration of tDCS ranged from 18 to 50 min, with total treatment ranging from 1 to 102 sessions. The main adverse events in children were almost identical to those in adults, namely, tingling (11.5%), itching (5.8%), redness (4.7%), and scalp discomfort (3.1%); in other words, the main adverse events in children were skin problems. Since the risk of inducing maladaptive neural plasticity may be higher during development than in adulthood (Vicario and Nitsche, 2013), however, we should perform further studies on the possibility of long-lasting cognitive changes (Davis and van Koningsbruggen, 2013; Andrade et al., 2014).

Recently, Ekici (2015) reported a pediatric case of seizure after tDCS. The patient was a 4-year-old boy with idiopathic infantile spasm and spastic tetraparesis whose seizures were controlled by anti-epileptic drugs. To reduce spasticity and improve upper limb function, anodal tDCS at 1.2 mA (25 cm^2 electrodes) was applied to the right motor cortex for 20 min. The patient had a seizure four hours after the last of three sessions. The author speculated that a recent adjustment in the patient's anti-epileptic treatment regimen, premedication with escitalopram, or anodal tDCS might have contributed to seizure generation in this patient (Ekici, 2015). Although it is unclear whether tDCS was truly responsible for inducing the seizure in this case, we may need to consider the possibility of seizure induction when applying tDCS, especially in children.

Even taking all the evidence together, serious adverse effects of tDCS within the standard protocols have rarely been reported. On the other hand, persistent skin lesions such as burn-like lesions and contact dermatitis are sometimes observed even in healthy subjects, which would be non-serious adverse effects. In addition, treatment-emergent mania or hypomania can occur in patients with unipolar and bipolar depression, whereas the causal relationships between tDCS and psychological changes are uncertain. Although there is one report of seizure, the causal relationship is unclear. Indeed, in a rat seizure model, Liebetanz et al. (2006) reported that seizure threshold was not reduced by anodal tDCS (Liebetanz et al., 2006). tDCS within the standard protocols is considered safe for both adults and children and for both healthy subjects and patients (Nitsche and Paulus, 2001, 2015; Nitsche et al., 2003a,b; Arul-Anandam et al., 2009; Borckardt et al., 2011, 2012; Peruzzotti-Jametti et al., 2013; Bennabi et al., 2015; Gillick et al., 2015; Ho et al., 2015; Krishnan et al., 2015; Matsumoto and Ugawa, 2015; Meron et al., 2015; Moliadze et al., 2015; Oberman and Enticott, 2015; San-Juan et al., 2015; Smit et al., 2015; Xu et al., 2015; Aparício et al., 2016; Arumugham et al., 2016; Bikson et al., 2016; Cha et al., 2016; Gbadeyan et al., 2016; Hu et al., 2016; Muszkat et al., 2016; Palm et al., 2016; Rubio et al., 2016; Shivakumar et al., 2016; Woods et al., 2016). Yet it remains important to be aware of the potential adverse effects of tDCS.

1.2. Adverse events of tACS

Antal et al. (2008) performed tACS at an intensity of 0.4 mA for 5–10 min at 1, 10, 15, 30 and 45 Hz for healthy subjects. The stimulus electrode (4 cm × 4 cm) was located over the motor cortex and the reference electrode (5 cm × 10 cm) over the contralateral supraorbital area. They reported that healthy subjects often perceived retinal phosphenes or flashes in their visual field (Antal et al., 2008). Kanai et al. (2008) reported that phosphene perception peaked at frequencies between 10 and 20 Hz (Kanai et al., 2008). At higher frequencies beyond about 40 Hz, subjects did not perceive phosphenes (Moliadze et al., 2010; Chaieb et al., 2011; Turi et al., 2013). Stronger phosphenes were elicited when electrode montages were closer to the retina (Kanai et al., 2008; Schutter and Hortensius, 2010; Turi et al., 2013). In addition, healthy subjects often felt cutaneous perceptions during tACS, although this occurred less often at higher frequencies (Ambrus et al., 2010; Turi et al., 2013). Raco et al. (2014) prospectively investigated the adverse events of tACS in healthy subjects. First, they investigated phosphene perception, dizziness, skin sensation, and pressure perception during eight seconds of stimulation using different frequencies (2 Hz, 4 Hz, 8 Hz, 16 Hz, 32 Hz, 64 Hz), intensities (1.5 mA, 1 mA, 0.5 mA, 0.25 mA), and montages (F3/F4, F3/C4, F3/P4, P3/F4, P3/C4, P3/P4) in 15 healthy subjects. Phosphene perception was most common and strongest with anterior montages and higher frequencies (phosphene perception was strongest at 16 Hz). Although phosphene perception could originate in the retina or visual cortex (Schwiedrzik, 2009), electrical field modeling studies have provided further evidence that the flickering following tACS was of retinal rather than cortical origin (Laakso and Hirata, 2013). Dizziness was strongest with posterior montages and at a frequency of 4 Hz, probably due to the involvement of the vestibular nerve. Skin sensation was most likely when tACS was performed at the anterior montages, whereas pressure perception was most likely at the posterior montages. All parameters had some influence on the probability and intensity of skin sensation (Raco et al., 2014). In keeping with these results, earlier studies on the electrical stimulation of skin had revealed that high stimulus intensity and frequency resulted in more perceptible skin sensation (Tuckett, 1982). Raco et al. (2014) also investigated the changes in sensations during long tACS protocols (2 Hz and 16 Hz, 1 mA, 60 s, F3/F4 and P3/P4) in 10 healthy subjects. They found that none of the sensations (i.e., neither phosphene perception nor dizziness nor skin sensation nor pressure perception) were modified during long periods of tACS (Raco et al., 2014).

Chaieb et al. (2014) investigated the safety of tACS at relatively high frequencies. When 5 kHz tACS was applied at an intensity of 1 mA for 10 min over the hand motor area, sustained changes in cortical excitability were observed (Chaieb et al., 2011). No aberrant changes after tACS were seen in NSE, EEG, or MRI in 18 healthy subjects. No subjects perceived heating under the electrodes or phosphenes. Therefore, a protocol consisting of tACS at 5 kHz was determined to be safe (Chaieb et al., 2014). Naro et al. (2016) administered cerebellar tACS at an intensity of 2 mA for 5 min over the right cerebellar hemisphere at frequencies of 10, 50, and 300 Hz. In their study, none of the participants had any adverse events (Naro et al., 2016a). Heise et al. (2016) reported that sensory discomfort was milder with the center-ring montage than with the classical electrode montage in tACS (20 Hz, 0.4 mA, 10 minutes) (Heise et al., 2016). In the center-ring montage, the target electrode is placed over the hand motor area and surrounded by the ring electrode; in the classical electrode montage, two electrodes are placed between the hand motor area and the contralateral supraorbital area. tACS has also been applied to children, and no serious adverse events have been reported (Alon et al., 1998; Krishnan et al., 2015).

A specific type of tACS known as the transorbital type has also been employed (Gall et al., 2010, 2016). In transorbital-type tACS, four stimulus electrodes are positioned at or near the eyeballs and one electrode is positioned at the occipital pole as the reference electrode. Transorbital-type tACS has the potential to modulate neuronal activity in the visual system at specific frequencies. Transorbital-type tACS with current bursts (5–20 Hz,<1 mA) improved visual acuity and increased the size of the visual fields

in both eyes in patients with optic nerve lesions (Fedorov et al., 2011). Gall et al. (2016) conducted a multicenter, prospective, randomized, double-blind, sham-controlled trial of transorbital-type tACS. 8–25 Hz transorbital-type tACS was administered at a 125% phosphene threshold intensity for 50 min per day over a total of 10 days. All adverse events were transient: skin sensation (active vs. sham tACS group: 12 vs. 8 patients), mild headache (4 vs. 2 patients), vertigo (2 vs. 1 patients), dizziness (1 vs. 0 patients), and back pain and stiff neck (1 vs. 0 patients). In this stimulation technique, no serious adverse effects were reported (Fedorov et al., 2011; Gall et al., 2016).

To date, all reported adverse events of tACS have been transient rather than persistent. No serious adverse effects have been reported in either healthy subjects or patients (Fedorov et al., 2010, 2011; Gall et al., 2010, 2016; Tadini et al., 2011; Abd Hamid et al., 2015; Kallel et al., 2016; Klimke et al., 2016; Nakazono et al., 2016; Naro et al., 2016b; Raco et al., 2016; Woods et al., 2016; Wu et al., 2016). The specific adverse effect would be phosphene perception. Although tACS, unlike tDCS, has not been reported to induce persistent adverse events, the adverse events of repetitive tACS application or even isolated sessions of tACS have not been fully clarified. Therefore, further investigations are required to establish the safety of tACS in humans.

2. Conclusions

tDCS and tACS are noninvasive tools to modulate neural activity in the human brain using weak electrical currents. Research in this field is accumulating rapidly. As the number of publications increases, the need for safety-oriented reviews grows stronger. In the near future, the International Federation of Clinical Neurophysiology is expected to publish guidelines on how to perform tDCS and tACS safely and effectively, based on the findings from a workshop on the safety of transcranial electric stimulation held on September 6–7, 2016, in Göttingen, Germany. The aim of this article is to summarize the potential adverse events of tDCS and tACS. This knowledge, used alongside the new guidelines from Clinical Neurophysiology, will enable practitioners to administer tDCS and tACS safely.

Conflict of interest

The authors report no conflicts of interest.

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