

Safety of Non-Invasive Brain Stimulation delivered via the Halo Neurostimulation System in Healthy Human Subjects

Halo Neuroscience

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ABSTRACT: Transcranial electrical stimulation (tES) is a technique that is increasingly used to modulate cortical excitability and induce neural plasticity in the human brain. Two prominent types of tES are transcranial direct current stimulation (tDCS) and transcranial variable frequency stimulation (tvFS). Over a period of two years, 1010 human subjects received tES directed to motor and/or non-motor cortical areas using the Halo Neurostimulation System, a novel neurostimulation device. This paper summarizes safety and describes the adverse event profile of tES, specifically tDCS and tvFS, observed in this series. Each of the 1010 subjects was assessed post-stimulation to identify adverse events. In addition to general assessment, subjects were specifically queried and results tabulated for any scalp burning (i.e., lesion), headache, scalp pain, and seizure. Mild sensation due to stimulation (e.g., tingling or itching) was not tabulated unless reported as scalp pain or causing withdrawal from the study. A total of 557 subjects received active stimulation, while 453 subjects received sham stimulation. The most commonly reported adverse event was headache (2.0% in active stimulation group and 3.8% in sham group). Scalp pain was also reported in 1.1% of subjects in the stimulation group and in 0.67% of the sham group. Withdrawal due to unpleasant sensation occurred in 0.54% of subjects receiving active stimulation. There were no reports of burns or seizure. Our results suggest that tDCS and tvFS can be safely applied to motor and non-motor cortical areas using the Halo Neurostimulation System in healthy humans.

INTRODUCTION

In the past 20 years, transcranial electrical stimulation (tES) has emerged as a useful technique in clinical neuroscience due to its ability to modulate corticospinal excitability and induce neuroplasticity in motor and other cortical regions. Several tES strategies aimed at modifying cortical excitability have been developed and frequently practiced over this time. Two such promising techniques are transcranial direct current stimulation (tDCS) and transcranial variable frequency stimulation (tvFS).

Transcranial direct current stimulation (tDCS) involves the application of a weak electrical current via two surface electrodes, an anode and a cathode. Animal studies (Jaberzadeh *et al.* 2013) and modeling work (Radman *et al.* 2009) suggest that anodal stimulation depolarizes excitatory neurons by increasing the resting membrane potential and hyperpolarizes inhibitory neurons by decreasing the resting membrane potential, while cathodal stimulation has the opposite effect. Thus, anodal tDCS is believed to generally increase cortical excitability while cathodal tDCS is be-

lieved to generally decrease it. These changes can last for hours or days after application of tDCS (Waters-Metenier *et al.* 2014). Studies on electrode placement indicate that modulatory effects are somewhat focal, allowing for effective stimulation of distinct brain regions. For example, multiple studies have found that tDCS over the primary motor cortex (M1) can produce long-lasting effects on motor learning (Waters-Metenier *et al.* 2014). Other studies have shown that tDCS over the dorsolateral prefrontal cortex (DLPFC) can produce long-term improvements in memory and cognitive function (Fregni *et al.* 2005).

Like tDCS, transcranial variable frequency stimulation (tvFS) is a form of tES. It involves the application of current in the form of a band-limited multi-frequency signal, such as random or pseudo-random noise, to the scalp over the target cortical region. The frequency is typically limited to lower than 640 Hz. High frequency tvFS (i.e., a band-limited signal with components between 100 and 600 Hz) generally increases cortical excitability while lower-frequency tvFS does not induce significant alterations (Terney *et al.* 2008). The mechanism by which tvFS influences cortical ex-

citability is not precisely known, but is thought to involve repeated and/or synchronous opening of Na⁺ channels, thereby increasing sensitivity of neuronal networks to modulation (Jaberzadeh *et al.* 2013). Because tVFS can induce less scalp sensation than other forms of brain stimulation, it has attracted increasing interest in recent years. tVFS has the ability to increase motor cortex excitability (Terney *et al.* 2008) and has been shown to improve motor skill learning (Prichard *et al.* 2014). VFS applied over the posterior parietal cortex (PPC) has also been shown to improve target discrimination (Cappelletti *et al.* 2013).

tDCS and tVFS have been frequently used to modulate cortical excitability and are generally considered safe. Parameters potentially affecting safety of brain stimulation include the strength of current, the size of the electrodes, and the duration of the stimulation. An MRI study found that conventional tDCS protocols do not induce brain edema or changes in the blood-brain barrier or cerebral tissue (Nitsche *et al.* 2007). tES does not have adverse effects on cognitive and psychomotor measures (Iyer *et al.* 2005).

Poreisz *et al.* (2007) synthesized the risks and adverse effects associated with tES based on a review of 567 stimulation sessions from 102 participants. The most commonly reported adverse effect was tingling (70% of participants), with a small proportion of participants reporting the sensation as burning (22%) or pain (18%). Participants described the burning or pain as quite mild (under 2 on a 5-point scale from zero to maximum intensity). The next most common adverse effect was fatigue (35%) followed by headache (10%). The authors suggest that fatigue could likely be due to the prolonged and uninteresting tasks required of the study. Headaches were also characterized as mild, and there was no evidence of any change in frequency or severity of headaches caused by tDCS. In this series of healthy, psychiatrically stable participants, 0% experienced nausea, mood changes, or seizure.

Despite the existence of this literature, additional data are always useful, and in the process of developing advanced technology to deliver tES it is important to collect extensive safety data. In the present report, we summarize observations from more than a thousand stimulation sessions completed in our lab. Stimulation included tDCS over M1 and left DLPFC as well as tVFS over M1 and rPPC. We delivered stimulation according to parameters common to most tES research, and results of our analysis are consistent with existing knowledge regarding the safety profile of tES.

EXPERIMENTAL DESIGN

Participants and Methods

We analyzed data from studies conducted between 2013 and 2015 that administered tDCS or tVFS over various scalp / cortical regions in 1010 healthy human participants. Subjects received either active stimulation ($n=557$) or sham stimulation ($n=453$). The mental and physical health of subjects was assessed prior to enrollment. All subjects gave written informed consent in accordance with applicable regulations and California Health and Safety Codes 24172 and 24173. The protocols were approved by MidLands Institutional Review Board.

In these studies, three cortical areas were stimulated: the motor cortex (M1), the left dorsolateral prefrontal cortex (DLPFC), and the right posterior parietal cortex (rPPC). Following stimulation, subjects completed a health assessment, including assessment for any adverse events, and were asked a series of questions regarding occurrence of any adverse events during stimulation.

Neurostimulation

All studies were conducted using the Halo Neurostimulation System. The electrodes were rectangular 6.4 x 4.4 cm sponges yielding a nominal contact region of 28 cm². Prior to administration, sponge contact surfaces were soaked in normal saline (0.9% NaCl). The intensity of stimulation varied between 1.1 mA and 2 mA for tDCS. For tVFS, stimulation current was defined by band-limited pseudo-random noise with spectrum 100-600 Hz, and the maximum stimulation delivered had 1 mA root-mean-square (RMS) amplitude. The duration of stimulation ranged from 13 to 30 minutes. tDCS stimulation sessions always included a gradual current increase over 30 seconds at the beginning of the session and a gradual current decrease over 30 seconds at the end of the session. For the sham condition, stimulation was provided exactly as in the treatment group, except that stimulation was only delivered for the first 30 seconds of the training block. Maximum current density at the stimulation electrodes was 0.07 mA/cm². This density is well below that which has been shown to cause brain tissue damage in animals in laboratory studies (25mA/cm², McCreery *et al.* 1990) and is similar to that used in prior published studies (0.0-0.066 mA/cm², Bastani & Jaberzadeh 2012). Comparable stimulation settings have been tested in multiple clinical trials and have proven to be safe in this subject population (Vines *et al.* 2008, Katak *et al.* 2012).

Target area	Active	Reference
Primary motor cortex (M1)	C3	C4
	C4	C3
	Cz	Right shoulder
Left dorsolateral prefrontal cortex (DLPFC)	F3	Right supra-orbital area
Right posterior parietal cortex (rPPC)	P4	P3

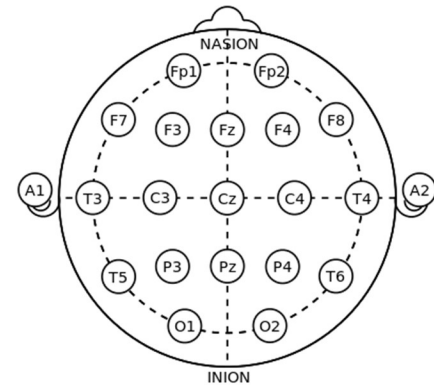


Table 1: Placement of tDCS/tVFS electrodes.

Electrode Placement

During motor cortex stimulation, electrodes were positioned over the left and right M1 for upper body experiments. This montage corresponds to areas C3 and C4, respectively, according to the International 10/20 system for EEG placement. Anode and cathode placement varied between left and right M1 depending on experimental design. Motor cortex studies involving stimulation of the lower body included anode placement over the leg region of M1 (Cz in the 10/20 system) and an adhesive electrode patch applied to the right shoulder acting as the cathode.

In the case of left DLPFC stimulation, the anode was placed over the left dorsolateral prefrontal cortex and the cathode was positioned over the right supra-orbital area. This montage corresponds to having the anode at the 10/20 F3 position, and the cathode on the forehead over the right eyebrow.

Finally, when stimulation was administered over the rPPC, the anode was placed over the right posterior parietal region and the cathode was placed over the left posterior parietal region. In terms of the 10/20 system, this montage corresponds to having the anode over P4 and the cathode over P3. The various electrode placements are summarized in Table 1.

Data Analysis

At the end of each session, each subject underwent a safety assessment to identify adverse events. In addition to general assessment, subjects were specifically queried and results tabulated for any scalp burning (i.e., lesion), headache, scalp pain, and seizure. Since mild sensations due to stimulation such as tingling and itching are frequent, generally accepted, and by now well-known in the literature (e.g., 70.6% incidence of tingling in Poreisz *et al.* 2007), these sensations were not tabulated unless described

by the subject as scalp pain or causing withdrawal from the study. Similarly, mild or moderate fatigue due to demanding or boring experimental tasks is well-known in the tES literature (e.g., 35.3% incidence in Poreisz *et al.*) and was not tabulated. Adverse event rates were characterized separately for subjects who received actual stimulation and subjects who received sham stimulation, and compared between these groups using the one-tailed Fisher's Exact test.

RESULTS

We analyzed safety data from 1010 subjects who received tES in our laboratory. There were zero reports of burn or seizure across all 1010 subjects, zero serious or unexpected adverse events, and zero withdrawals due to adverse events other than unpleasant sensation. Table 2 summarizes incidence of headache, scalp pain, or withdrawal due to unpleasant sensation after stimulation of either M1, DLPFC, or rPPC. Incidence was compared between sham and stimulation groups by calculating the one-tailed *p*-values for each comparison with the 2x2 Fischer's Exact tests. One-tailed *p*-values were used since these are more conservative in this situation; i.e., the one-tailed values attribute greater significance to any relationship between stimulation and adverse event rates.

All *p*-values were > 0.05, meaning that no event type could be definitively attributed to the effects of stimulation when analyzed across brain regions. The most commonly reported adverse event was headache, reported by 29 subjects (12 stimulation, 17 sham). The next most common adverse event was scalp pain, reported by 9 subjects (6 stimulation, 3 sham). Withdrawal due to unpleasant sensation occurred in just 3 subjects (3 stimulation, 0 sham).

Besides analyzing safety data across brain and scalp regions, we also analyzed adverse events and with-

	Total (N)	In stimulation group	In sham group	<i>p</i>
M1	706	396	310	-
headache	19	6	13	0.9923
scalp pain	9	6	3	0.3860
withdrawal due to unpleasant sensation	1	1	0	0.5609
DLPFC	285	151	134	-
headache	10	6	4	0.4511
scalp pain	0	0	0	1.000
withdrawal due to unpleasant sensation	2	2	0	0.2798
rPPC	19	10	9	-
headache	0	0	0	1.000
scalp pain	0	0	0	1.000
withdrawal due to unpleasant sensation	0	0	0	1.000
Total	1010	557	453	-
headache	29	12	17	0.9554
scalp pain	9	6	3	0.3641
withdrawal due to unpleasant sensation	3	3	0	0.1673

Table 2. Adverse events reported after tES, divided by brain region. *p*-values were calculated using one-tailed Fisher's Exact test for the comparison between stimulation and sham groups. No adverse events correlated definitively with stimulation (all *p* > 0.05).

drawals across stimulation type. Table 3 summarizes the effects in terms of stimulation type - i.e., tDCS or tVFS. Neither tDCS nor tVFS produced *p*-values < 0.05 for the comparison between stimulation and sham.

DISCUSSION

This purpose of this work was to characterize the safety profile of tDCS and tVFS delivered via the Halo Neurostimulation System, and add further to the body of knowledge regarding tES safety. We analyzed adverse events related to stimulation in 1010 human subjects, as determined by experimenter assessment and a quantitative self-report at the end of each stimulation session. Our analysis suggests that tDCS applied to M1, DLPFC and rPPC is safe and is associated with a low incidence of adverse events.

Previous research (Poreisz *et al.* 2007) has shown that the most common effect of tES is a mild tingling sensation (~70%), often felt as a mild burning or itching sensation. Fatigue is another very commonly reported effect (~35%) in tES studies, thought to be due to boring or tiring experimental protocols. Since these mild events have been well documented in prior research, we did not tabulate them quantitatively. Thus, the primary intent of the data collection in our protocol was to capture any adverse events that would impact safety - including specifically tabulating headache or scalp pain, any lesions or burns, any seizure, and

withdrawal due to unpleasant sensation. Note that no withdrawals occurred due to any other adverse event.

There were no burns or seizures, and no other serious or unexpected adverse events. The most commonly reported event was headache, occurring in 29 subjects (2.9%). Note that headache was somewhat more prevalent in subjects receiving sham stimulation (1.7%) versus subjects receiving real stimulation (1.2%), although the difference did not reach significance. This suggests, however, that the incidence of headache was due more to the natural effect of performing demanding cognitive or motor tasks with snug-fitting headwear, or to pre-existing causes, than to any effect of the stimulation itself.

Scalp pain was the second most common adverse event, reported in 9 subjects (0.9%). In addition, there were three withdrawals due to unpleasant sensation (0.3%). While the *p*-values for scalp pain and withdrawal due to unpleasant sensation do not definitively show a linkage with stimulation, it is likely that this (infrequent) discomfort is at least partially due to stimulation, since stimulation induces some sensation in most people. It is also likely that this discomfort is also partially due to prolonged physical pressure of electrodes on the scalp.

Finally, since these were sham-controlled, double-blind studies, we completed a blinding (detectability)

	Total (N)	In stimulation group	In sham group	p
tDCS	858	468	390	-
headache	23	9	14	0.9570
scalp pain	7	5	2	0.6081
withdrawal due to unpleasant sensation	3	3	0	0.1618
tVFS	152	89	63	-
headache	6	3	3	0.8048
scalp pain	2	1	1	0.8298
withdrawal due to unpleasant sensation	0	0	0	1.0000

Table 3: Adverse events reported after stimulation, divided by stimulation type. No adverse events were correlated with either type of stimulation ($p < 0.05$).

analysis to determine the effectiveness of our blinding procedure. Only 50.77% of subjects were able to correctly identify which type of stimulation they received, supporting the validity of our safety and other data.

CONCLUSION

Transcranial electrical stimulation (tES) is an exciting frontier in clinical neuroscience due to its ability to modulate cortical excitability and alter neuronal plasticity. tDCS and tVFS are two prominent forms of tES that are currently under investigation as treatments for both clinical and healthy populations. The purpose of this work was to better characterize the safety profile of tDCS and tVFS delivered via the Halo Neurostimulation System. Our results indicate that stimulation administered by the Halo system has a favorable safety profile and is associated with a very low incidence of adverse events, with no unexpected or serious adverse events.

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