

tDCS clinical research - highlights: Safety of transcranial Current Stimulation

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Is transcranial current stimulation (tCS, including direct current, tDCS, alternating current, tACS, or random noise stimulation tRNS) safe? Under what conditions?

Our findings from the literature search performed agree with recent reviews on the subject and with our prior appraisal in 2012. **There continues to be a lack of observations on anything but small side effects (redness, tingling, etc.).**

With regard to safety, application of tDCS with the protocols used to date appears to be safe [[Poreisz2007a](#), [Brunoni2011a](#)]. As stated in the review by Nitsche et al [[Nitsche2008](#)],

Extensive animal and human evidence and theoretical knowledge indicate that the currently used tDCS protocols are safe. However, knowledge about the safe limits of duration and intensity of tDCS is still limited. Thus, if charge or current density is exceeded greatly beyond the currently tested protocols, which might be desirable, for example, for clinical purposes, we suggest concurrent safety measures.

tDCS has been tested in thousands of subjects worldwide with no evidence of toxic effects to date. In addition to the hundreds of studies exploring tDCS effects in diverse contexts, some studies have focused specifically on safety.

The accumulated experience in the last four decades has demonstrated that tDCS is associated with only mild and transient side-effects (both in normal volunteers and in individuals with varied neuropsychiatric disorders). The adverse effects most commonly associated with by tDCS include mild transient headache and mild transient pruritus and erythema in the stimulation site (the latter with a duration of less than 40 minutes). Other less prevalent side-effects include nausea, difficulty of concentration, visual phosphenes and vertigo.

Overall, these results are compatible with animal studies in the rat that indicate that current protocols are two orders of magnitude below analogous damage limits in the rat [[Liebetanz2009](#)].

As reported in the pivotal review by Brunoni et al [[Brunoni2011a](#)] the adverse effects of active vs. sham tDCS include

itching (39.3% vs. 32.9%, $p>0.05$), tingling (22.2% vs. 18.3%, $p>0.05$), headache (14.8% vs. 16.2%, $p>0.05$), burning sensation (8.7% vs. 10%, $p>0.05$) and discomfort (10.4 % vs. 13.4 %, $p>0.05$).

Our review extends Brunoni's, covering papers up to 2012. As reported in [[Stagg2011b](#)],

More than 100 studies have been performed using tDCS in healthy controls and in patient populations, and no serious side effects have occurred (for a review, see Nitsche and others 2008). Slight itching under the electrode, headache, fatigue, and nausea have been described in a minority of cases in a series of more than 550 subjects (Poreisz and others 2007). Detailed studies have been performed to assess the safety of tDCS. These have shown that there was no evidence of neuronal damage as assessed by serum neuron-specific enolase after application of a 1 mA anodal current for 13 minutes (Nitsche and Paulus 2001; Nitsche, Nitsche, and others 2003) or MRI measures of edema using contrast-enhanced and diffusion-weighted MRI measures after application of a 1 mA current for 13 minutes (anodal) or 9 minutes (cathodal; Nitsche, Niehaus, and others 2004). No pathological waveforms were seen on EEG, and no worsening of neuropsychological measures was observed after frontal lobe stimulation with current intensities of up to 2 mA for 20 minutes (Iyer and others 2005). No heating occurred under the electrode during 20 minutes of 2 mA stimulation, even within the bore of a 7T MRI scanner (Stagg and others 2009).

In addition, a recent study was performed in rats using an epicranial electrode montage designed to be similar to that used in tDCS (Liebetanz and others 2009). This demonstrated that brain lesions occurred only at current densities greater than 1429 mA/cm² applied for durations longer than 10 minutes. In standard tDCS protocols in humans, a current density of approximately 0.05 mA/cm² is produced.

[[Paulus2011a](#)] indicates that tDCS applied with 1 mA needs larger electrodes than those used for electroencephalography in order to avoid skin burns: *Even when using electrode sizes of 35 cm², current application starts to become painful (Furubayashi et al., 2008) at 3 mA.*

Nevertheless, electrode positions above cranial foramina and fissures should be avoided because these could increase beyond safety limits the effective current density.

Other modalities of tCS have been less systematically studied, but no further reports of adverse side effects have been provided to date.

As pointed out by [[Brunoni et al. 2011](#)], the most severe AE found in healthy volunteers was skin lesions on the site the electrode was placed using a 2 mA current [[Palm et al. 2008](#)]. Along these lines, one study performed in 58 rats delivering different doses of electric current showed that brain damage only occurred at doses 100 times higher than used in humans [[Liebetanz2009](#)].

Although the following papers did not appear in our search, we include them for completeness. Occasionally, skin lesions have been described after tDCS [[Frank et al. 2009](#), [Palm et al 2008](#)]. These, however, were rare, and most probably caused by insufficient skin-electrode contacts or skin lesions antecedent to stimulation. As indicated in Frank et al., it should be possible to avoid the problem of accumulating concentrations of skin toxic substances with the use of sodium chloride solution, the regular replacement of the sponge, and the careful inspection of the condition of the skin under the electrode before and after tDCS.

Most studies have been carried out so far with 35 cm² electrodes and currents - in recent years - up to 2 mA without serious adverse effects. Current density delivered has varied between 0.029 and 0.08 mA/cm² in most published studies [Nitsche2008]. In the rat [Liebetanz2009] brain lesions occurred above densities of 4.29mA/cm² and 5.2400 C/cm². With a current density limit of 0.06 mA/cm², this dosage limit is reached after 24 hours of use.

With regards to tDCS in children and adolescents, a recent metaanalysis reports that it is safe, with reported adverse effects incidente as in adults:

Krishnan C, Santos L, Peterson MD, Ehinger M, Safety of noninvasive brain stimulation in children and adolescents., Brain Stimul. 2015 Jan-Feb;8(1):76-87.

Noninvasive brain stimulation (NIBS) techniques such as transcranial magnetic stimulation (TMS) and transcranial current stimulation (tCS) have the potential to mitigate a variety of symptoms associated with neurological and psychiatric conditions, including stroke, cerebral palsy, autism, depression, and Tourette syndrome. While the safety of these modalities has been established in adults, there is a paucity of research assessing the safety of NIBS among children. **OBJECTIVE:** To examine the existing literature regarding the safety of NIBS techniques in children and adolescents with neurologic and neuropsychiatric disorders. **METHODS:** An electronic search was performed on online databases for studies using NIBS in individuals less than 18 years of age. Non-English publications, diagnostic studies, electroconvulsive therapy, single/dual pulse TMS studies, and reviews were excluded. Adverse events reported in the studies were carefully examined and synthesized to understand the safety and tolerability of NIBS among children and adolescents. **RESULTS: The data from 48 studies involving more than 513 children/adolescents (2.5-17.8 years of age) indicate that the side effects of NIBS were, in general, mild and transient [TMS: headache (11.5%), scalp discomfort (2.5%), twitching (1.2%), mood changes (1.2%), fatigue (0.9%), tinnitus (0.6%); tCS: tingling (11.5%), itching (5.8%), redness (4.7%), scalp discomfort (3.1%)] with relatively few serious adverse events.** **CONCLUSION:** Our findings indicate that both repetitive TMS and tCS are safe modalities in children and adolescents with various neurological conditions, especially when safety guidelines are followed. The incidence of adverse events appears to be similar to that observed in adults; however, further studies with longer treatment and follow-up periods are needed to better understand the benefits and tolerance of long-term use of NIBS in children.

Use of smaller Ag/AgCl electrodes

In [Miranda2009] it was already argued that the ratio of injected current to area is not a good indicator of current density in the brain: *Numerical methods were used to calculate the current density distribution in a standard spherical head model as well as in a homogeneous cylindrical conductor. A non-linear relationship exists between the injected current, the electrode area and the current density at a fixed target point in the brain, which can be described in terms of a montage-specific I-A curve. I-A curves calculated using realistic head models or obtained experimentally should be used when adjusting the current for different electrode sizes or when comparing the effect of different current-electrode area combinations.*

There are now many studies using small electrodes (1 to 3 cm²) using conductive gels with Ag/AgCl electrodes at up to 2 mA of intensity without further remarks on Adverse Effects. In the last 3 years several new studies have been performed showing that the use of small electrodes with Ag/AgCl+gel interfaces is safe:

In [Murray2014a, Murray LM, Edwards DJ, Ruffini G, Labar D, Stampas A, Pascual-Leone A, Cortes M, Intensity dependent effects of tDCS on corticospinal excitability in chronic Spinal Cord Injury., Arch Phys Med Rehabil. 2014 Nov 22], nine subjects with chronic SCI and motor disfunction underwent 3 twenty minute sessions of tics with 1-2 mA using 3 cm² Pi electrodes (Starstim, Neuroelectrics). No adverse effects were reported with any of the experimental conditions.

In [Ruffini2015a, G. Ruffini, C. Martinez-Ruiz de Lara, I. Martinez-Zalacain, O. Ripolles, M. Subira, E. Via, G. Mitja, J. Munuera, J. M. Menchón, C. Soriano-Mas, Narcís Cardoner. Optimized multielectrode tDCS modulates corticolimbic networks. NYC Neuromodulation Conference (January 2015).], 20 healthy subjects underwent 20 minutes of stimulation twice with Pi electrodes (3 cm²) with no adverse effects (Starstim, Neuroelectrics).

In [Cortes2015, Cortes, M., Edwards, D., Putrino, D., Anodal tDCS decreases total EEG power at rest and alters brain signaling during fatigue in high performance athletes, Neuromodec 2015, NY], 4 athletes received 20 minutes of tDCS with Pi Electrodes (3 cm²) with no ill effects (Starstim, Neuroelectrics).

In [Boratyn et al [D. Boratyn, G. Ruffini, M. Cortes, A. Rykman, A. Medeiros, A. Pascual-Leone, D. Edwards. Focal tDCS in Chronic Stroke patients: A pilot study of physiological effects using TMS and concurrent EEG. Clinical Neurophysiology, Volume 124, Issue 10 , pp: 146-147 (October 2013)], . Fifteen chronic stroke patients with hemiparesis following a first single unilateral lesion received 20 min of bilateral 1 mA anodal tDCS over the motor cortex of the lesioned hemisphere. Bilateral M1 stimulation using small Ag/AgCl (Pi) electrodes is **well tolerated** and can augment corticospinal excitability in the affected hemisphere (Starstim, Neuroelectrics).

In [Faria2012a, [Faria P1, Fregni F, Sebastião F, Dias AI, Leal A., Feasibility of focal transcranial DC polarization with simultaneous EEG recording: preliminary assessment in healthy subjects and human epilepsy, Epilepsy Behav. 2012 Nov;25(3):417-25.] the authors investigate the feasibility of an experimental system for simultaneous transcranial DC stimulation (tDCS) and EEG recording in human epilepsy. They report tolerability of this system in a cross-over controlled trial with 15 healthy subjects and preliminary effects of its use, testing repeated tDCS sessions, in **two** patients with drug-refractory Continuous Spike-Wave Discharges During Slow Sleep (CSWS). The system combining continuous recording of the EEG with tDCS allowed detailed evaluation of the interictal activity during the entire process. Stimulation with 1 mA was well-tolerated in both healthy volunteers and patients with refractory epilepsy.

In [Minhas2010a, Minhas P, Bansal V, Patel J, Ho JS, Diaz J, Datta A, Bikson M. Electrodes for high-definition transcutaneous DC stimulation for applications in drug delivery and

electrotherapy, including tDCS. Journal of Neuroscience Methods. 2010;190:188-197.] different small electrode types (<1.2 cm diameter, or ~1.1 cm² area) were systematically tested in **8 subjects**. Anode and cathode electrode potential, temperature, pH and subjective sensation over time were assessed during application of 2 mA direct current, for up to 22 min on agar gel or subject forearms. *Examination of the skin after stimulation indicated transient redness. Overall, in cathodal stimulations there are higher chances of observing skin irritation in the form of small bumps or black dots (<1 mm) and apparent roughening of the skin under the electrode (Berliner, 1997; Geddes and Roeder, 2004). Observation of bumps or dots was not apparently correlated to subjective pain sensation, polarity or any physical gel changes. All effects on the skin were reversible and disappeared within few hours. No subject reported a lasting irritation or pain. Further, we note here that current density (current to electrode contact area) is not a good parameter to linearly extrapolate the magnitude of the generated electric fields (A) in the brain or discomfort (B).*

In [**Turi2014a, When Size Matters: Large Electrodes Induce Greater Stimulation-related Cutaneous Discomfort Than Smaller Electrodes at Equivalent Current Density. Brain Stimul. 2014 Feb 5]**, the authors examined the relationship between current density, current intensity and cutaneous sensations perceived during tDCS. Two experiments were performed. In the first control experiment, the cutaneous sensations induced by varying current intensities (0.025, 0.5, 1.0 and 1.5 mA) were examined up to 10 min. These data were used for optimizing inter-stimulation intervals in the second main experiment, where participants rated the intensity, spatial size and location of the cutaneous sensations experienced during tDCS using two electrode sizes (16 cm² and 35 cm²). In the equivalent current density condition, the current density was kept constant under both electrodes (0.014, 0.029 and 0.043 mA/cm²), whereas in the equal current intensity condition (0.5, 1.0 and 1.5 mA) the same intensities were used for the two electrode sizes. **Large electrodes were associated with greater cutaneous discomfort when compared to smaller electrodes at a given current density. Further, levels of cutaneous perception were similar for small and large electrodes when current intensity was kept constant.**

In [**Borkardt2012a, Borckardt JJ, Bikson M, Frohman H, Reeves ST, Datta A, Bansal V, Madan A, Barth K, George MS. A pilot study of the tolerability and effects of high-definition transcranial direct current stimulation (HD-tDCS) on pain perception. The Journal of Pain. 2012;13(2):112-120.]**, **twenty-four healthy** adult volunteers underwent quantitative sensory testing before and after 20 minutes of real (n = 13) or sham (n = 11) 2 mA HD-tDCS over the motor cortex (1 cm² electrodes). No adverse events occurred and no side effects were reported. Real HD-tDCS was associated with significantly decreased heat and cold sensory thresholds, decreased thermal wind-up pain, and a marginal analgesic effect for cold pain thresholds. No significant effects were observed for mechanical pain thresholds or heat pain thresholds. HD-tDCS appears well tolerated, and produced changes in underlying cortex that are associated with changes in pain perception.

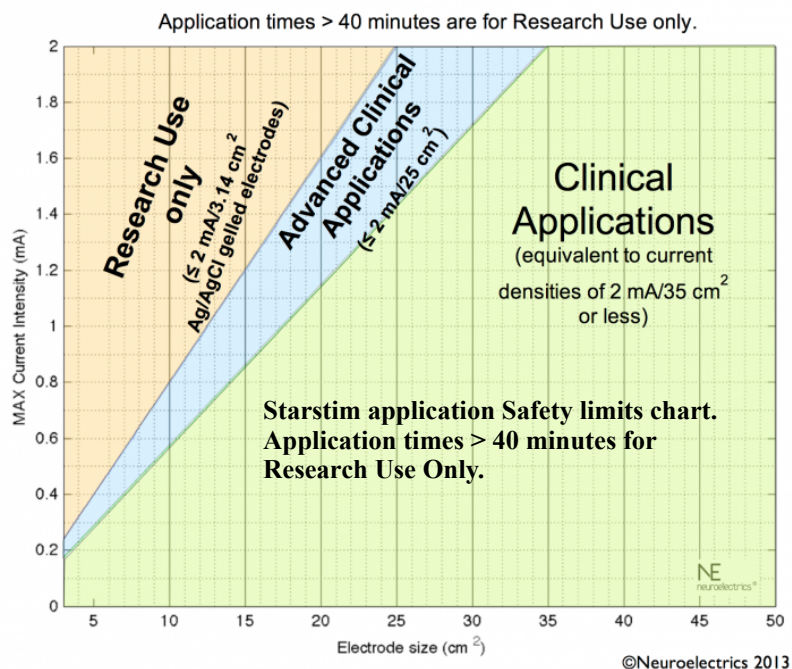
Both of these limits are about two orders of magnitude beyond current tDCS practice today.

Proposed warnings:

- tCS therapy should be supervised by a trained medical doctor.
- Modalities other than tDCS (tACS, tRNS) are for research purposes only.

- There are no studies in the literature describing the effects of direct current treatments on pregnant women, or children below 18 years, or patients with pacemakers, intracranial electrodes, implanted defibrillators, or any other prosthesis.
- Before applying Starstim, make sure that pacemakers, intracranial electrodes, defibrillators, or any other prosthesis are not implanted in the patient. Otherwise, the application of DC currents could be unsafe.
- For safety, **Starstim is limited in the following ways:** It will not operate if the contact impedance is above 20 kOhm. It can only provide potential differences across electrode of 30 V to deliver a maximum, at any electrode of (+ or -) 2 mA of current. We indicate that it is designed for use with Neuroelectrics' tCS compatible electrodes only.
- Based on abundant literature, the guideline for clinical use is to keep average current densities in electrodes below $2 \text{ mA}/35 \text{ cm}^2 = 0.06 \text{ mA}/\text{cm}^2$. Such stimulation current densities are far from the threshold for tissue damage ($14.3 \text{ mA}/\text{cm}^2$) recently indicated for tDCS in an animal model.
- Current densities above $0.06 \text{ mA}/\text{cm}^2$ (but always well below $14.3 \text{ mA}/\text{cm}^2$) are for advanced clinical or research purposes only.
- Stimulation session durations beyond 40 minutes are for research purposes only.
- In addition, electrode positions above cranial foramina and fissures should be avoided because these could increase beyond safety limits the effective current density.
- Starstim can only be used with specifically designed Neuroelectrics electrodes.
- With sponge electrodes, the use of sodium chloride solution, the regular replacement of the sponge, and the careful inspection of the condition of the skin under the electrode before and after tDCS is recommended.
- Observed Adverse Effects include: skin itching, tingling, headache, burning sensation and discomfort. In rare cases, skin lesions have been observed. If skin lesions are observed, the treatment must be suspended and the equipment revised.
- Starstim components must never be opened or damaged.
- Before using check that Starstim components, including electrodes, are undamaged and clean.

The following chart (updated 2015) will be provided to guide operators. It is an update or the 2012 one based on the accumulated experience with small Ag/AgCl electrodes by several groups).



It illustrates the MAX average current density that can be used for mainstream clinical applications, advanced clinical applications, research as a function of electrode size.

The proposed limits are not based on available negative evidence (i.e., findings of Adverse Effects with higher current densities). Rather, it is a conservative statement based on the current experience with current densities above 2 mA/35 cm²).

In summary, with the above, the proposed product literature and Instructions for Use is consistent with the clinical data and cover all the hazards and other clinically relevant information that may impact on the use of the device.