HOCHSCHULE FÜR ANGEWANDTE
WISSENSCHAFTEN HAMBURG
Hamburg University of Applied Sciences

FAKULTÄT FÜR MEDIZINTECHNIK
Department of Biomedical Engineering

"Extra-Low Voltage and Limited Total Energy Approaches to Increase Patient Comfort and Safety During Transcranial Direct Current Stimulation"

Bachelor Thesis

Written by:

Christoph Hahn

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Supervised by:

Prof. Dr.-Ing. Friedrich Ueberle
Prof. Marom Bikson, Ph.D.

Hochschule für Angewandte Wissenschaften Hamburg
Hamburg University of Applied Sciences

the City College of New York

I. Declaration

I, Christoph Hahn, declare that this thesis and the work presented in it are my own.
I confirm, that

- This work was compiled mainly while in candidature for a degree at this University.
- It is clearly stated where any part of this thesis or work have been submitted for a degree or any other qualification at this University or any other institution.
- Acknowledgements to publications and reference materials are noted in the text.
- The sources of citations and references are listed in the Bibliography. With the exception of such quotations, this thesis is entirely my own work.
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II. Abstract

Transcranial Direct Current Stimulation (tDCS) is a non-invasive brain stimulation technique aiming to polarize brain tissue in order to elicit modulating effects on cortical activity. During tDCS, weak constant current is applied across the brain through surface electrodes which are attached to the scalp. tDCS has shown promising therapeutic effects in a range of neurological conditions and is being evaluated for therapeutic use in epilepsy, major depression, chronic pain, stroke rehabilitation and more.

Though tDCS is a generally well tolerated treatment option, there is room for improvement of patient safety and comfort. During tDCS, current is constant and skin-electrode impedance is strongly dynamic. Thus, compliance voltage is also dynamic. Skin-electrode impedance may be influenced through choice of electrode type and the way of electrode preparation prior to treatment. High impedance and voltage during tDCS can co-induce skin burns at the electrode sites.

Here, feasibility of reduced (peak) voltage tDCS is investigated and presented alongside a rather protective and advanced new approach for voltage and current control during tDCS. According to the results, the maximum stimulator output voltage may be reduced significantly in the most common tDCS paradigms without affecting stimulation intensity and efficacy.

Optimized electrode preparation combined with reduced maximum stimulator output voltage and intelligent current waveforms is considered a viable contribution towards more safe, protective and reliable brain stimulation paradigms, especially avoiding the occurrence of skin lesions after multiple stimulation treatments.

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Content

1.Foreword

In modern medicine, new treatment techniques in pharmacology and biomedical engineering are constantly being developed and refined in order to enable treatment and healing of yet untreatable diseases, to increase patient safety and comfort in existing therapies and to reduce costs to broaden availability of advanced medical treatments.

Signal processing in the human body, i.e. in the nervous system, is based on electrochemical processes during the generation of action potentials, which form the actual signals. These processes can be influenced and modulated through pharmacological (chemical) agents *or through the application of electricity to the human body.* A figurative example for this is the application of electric pulses to the human heart through implanted cardiac pacemakers, assuring a steady and continuous heartbeat in patients suffering from cardiac arrhythmia.

This thesis is concentrated on the field of *electrical neuromodulation.* In neuromodulation, controlled effects on the activity of specified parts of the nervous system through application of electric currents are being used *to facilitate therapeutic effects in neurological diseases like epilepsy, chronic pain, Parkinson's, major depression and stroke*. Electrical neuromodulation can be administrated in different paradigms by a variety of techniques, both invasively and non-invasively. Neuromodulation techniques can be aimed at the brain, spinal cord or peripheral nerves.

Here, an experimental work on safety-parameter optimization of a non-invasive brain stimulation technique named transcranial Direct Current Stimulation (tDCS) is presented and preceded by necessary theoretical background.

2.Theoretical Background

2.1. What Is tDCS and Why Is it Interesting for Use in Medicine?

Transcranial Direct Current Stimulation (tDCS) is a stimulation technique aiming to electrically polarize brain tissue in order to modulate the activity of certain brain areas. During tDCS, a weak constant current is applied across the brain to achieve such modulation of brain activity. Usually current magnitudes between 1 mA and 2.5 mA are used to administer tDCS. Current is being applied to patient's scalps for durations of up to 20 minutes and longer in daily sessions, sometimes over several weeks. tDCS involves the use of at least two surface electrodes (one anode and one cathode) to deliver a stimulating current to the patient. The anode is conventionally known as the positively charged electrode, while the cathode is negatively charged. Electrical current flows in the direction from cathode to anode. During stimulation, surface electrodes are connected to a battery driven stimulator device, which is a constant current source that allows adjustment of at least current magnitude and stimulation duration. A notable feature of *Transcranial* Direct Current Stimulation is that it is a *non-invasive* way of modulating brain activity. Due to very weak currents and the non-invasiveness of tDCS, this technique is only suitable for modulation of the cerebral cortex, the most outer part of the brain, which lies closest to the surface electrodes attached to the patient's head. Deep brain areas cannot be reached with sufficient electrical intensity to achieve controlled modulation effects.

In recent years, scientific and clinical interest in tDCS has evolved rapidly, after Priori et al. (1) and Nitsche & Paulus (2, 3) were able to demonstrate the effects of direct current polarization of the human motor cortex. In these studies, it was shown that stimulation of the human motor cortex with weak DC can alter the amplitude of motor evoked potentials. Motor evoked potentials (MEP) can be elicited using a technique called Transcranial Magnetic Stimulation (TMS) and are a suitable method to gain information about neuronal excitability of the motor cortex. Priori et al. demonstrated that, even using very small dosage of DC stimulation (repeated 7 second pulses, ≤ 0.5 mA) controllable and reproducible effects on cortical excitability can be elicited. Nitsche & Paulus could show a dependency of modulation effects on *stimulation polarity*. This means that depending on which electrode is used to stimulate the motor cortex, the MEP amplitude will either be increased or decreased. It has been found, that anodal stimulation of the motor cortex

leads to increased MEP sizes while cathodal stimulation of the motor cortex leads to decreased MEP sizes. Due to these findings it has become usual to speak of anodal tDCS (which is considered to be *exciting* neuronal activity) or cathodal tDCS (which is considered to be *inhibiting* neuronal activity), *depending on the electrode polarity applied to the field of interest*. For example, if tDCS is administered with one cathode over the primary motor cortex (also called M1) and one anode over the contralateral orbit, this could be called cathodal M1-tDCS. Of course in every tDCS session, there is at least one anode and at least one cathode involved to complete the electrical circuit. When choosing electrode positions clinicians always have to take into account *both* electrodes with the possible effects they may have on underlying brain tissue. Position and distance between electrodes play an important functional role in quality and quantity of tDCS-effects (4).

Nitsche & Paulus not only showed the polarity dependency of the effects of tDCS, they also found out that the effects of DC polarization can outlast the end of stimulation for several minutes – thus it may be spoken of acute affects (while DC is switched on) and after effects (after DC is switched off) of tDCS. Moreover, it has been found that the effect size of acute and after effects depends on applied current magnitude and stimulation duration. 'Effect size' is the relative change of MEP amplitude compared to baseline *and* the duration of the effect after DC stimulation has been switched off. For example a 10 minute 1mA tDCS-session compared to a 20 minute 1mA tDCS-session will produce smaller MEP changes which will vanish faster. These findings were a first hint that the effects of tDCS are *cumulative*.

The experiments of Priori and Nitsche & Paulus were the beginning of a rapidly growing interest in tDCS by research and clinical groups. Examples like the treatment of Parkinson's disease with electrical stimulation show that there is *a reasonable expectation that electricity, if applied in the correct way to the right parts of the human nervous system, can have strong healing power to multiple kinds of neurological conditions.* Various techniques have been developed to apply electrical current to the human brain. Those include Deep Brain Stimulation (DBS), Transcranial Magnetic Stimulation (TMS) and Electroconvulsive Therapy (ECT):

DBS is a highly specialized technique which involves the implantation of a pulse generator below the clavicle and of stimulation electrodes and connection leads into deep brain areas like the basal ganglia, especially the subthalamic nucleus. Great success has been achieved using DBS as a treatment of Parkinson's disease symptoms (5), and recently also in patients suffering from major depression (6). While DBS is a very direct and effective way of applying current to the brain, it is also highly invasive as it requires

brain surgery to be installed and initiated. Thus DBS is a technology which bears the risk and extremely high cost of brain surgery.

TMS is a different stimulation approach where an external magnetic coil, connected to an electronic control circuit, is used to induce a pulsed current in the human cortex and thus depolarize neuron populations. Depending on the type of application, TMS can be applied with just a single pulse or with large numbers of repeated pulses (repetitive TMS = rTMS). (r)TMS has shown to be useful for diagnosis of the motor system by eliciting MEPs and is being reviewed for the treatment of major depression (7-9), stroke rehabilitation (10) and Parkinson's disease (11). TMS is a noninvasive technique for cortical stimulation which causes smaller risk to the patient and makes it more easily applicable than DBS. TMS requires expensive control electronics and is therefore a rather high-cost medical tool.

ECT is an electrical treatment option mainly used for patients suffering major depression and who are non-responsive or intolerant of pharmacological antidepressants. ECT involves the application of very intense electric pulses (incomparable to tDCS, DBS, TMS) through surface electrodes in order to generate seizures in the brain. ECT has shown to be an effective treatment for this group of patients (12), though is highly controversial due to its adverse effects, especially on memory and cognition (13, 14).

Looking at these three examples of electrical brain stimulation and at the results of Priori and Nitsche & Paulus it becomes clear why clinicians and researchers put high hopes into future clinical use of tDCS:

Unlike believed before, weak direct current, applied non-invasively through surface electrodes, is strong enough to elicit *significant and controllable effects on cortical activity*. tDCS is thus a promising therapeutic approach for a range of neurological (cortical) conditions. Non-invasiveness and low electrical power make tDCS a rather safe and comfortable experience for both the patient and the operator. Simple electronics keep the cost for tDCS hardware lower than most competitive pharmaceutical therapies and other stimulation technologies like DBS or TMS. Applied in a simple setup, tDCS is even thinkable as a home therapy. Due to these promising aspects, clinical trials are currently ongoing for use of tDCS as a therapy in major depression, epilepsy, chronic pain, stroke rehabilitation and more.

In order to exemplify which therapeutic effects can be induced by application of tDCS, a small sample of clinical tDCS results is summarized here:

- Hummel et al. tested anodal tDCS on stroke patients suffering from post-stroke paresis (15). Patients who received real-tDCS of a hand-associated motor cortex area (compared to the sham-tDCS control group - see below for 'sham-tDCS') showed a significant motor function improvement of the right paretic hand. This was tested by a widely accepted motor function test using fine motor tasks like turning over cards or picking up beans with a spoon, representing everyday challenges for paretic patients. Improved motor function was found in every single real-tDCS patient and outlasted the stimulation period. This study suggested that tDCS may have beneficial effects on motor function in post-stroke paretic patients. Numerous studies are ongoing to evaluate tDCS use in stroke patients – not only for improvement of motor function but also in cases of post-stroke aphasia (16).
- A tDCS-trial in thirty-two patients suffering from Fibromyalgia was conducted by Fregni et al. (17). Here, anodal motor cortex tDCS was tested for beneficial effects on chronic muscle and connective tissue pain which subjects were suffering. DC stimulation of the primary motor cortex led to "a larger, significant improvement of pain compared with sham stimulation. This effect is specific to the site of stimulation and can last for several weeks after treatment with stimulation has ended" (17). Trials investigating tDCS as a pain relieving therapy in general and for fibromyalgia specifically are currently ongoing.
- Antidepressant effects of DC stimulation were tested by Boggio et al. in a clinical trial with 40 patients suffering from major depression (18). Anodal tDCS of the left dorsolateral prefrontal cortex (DLPFC - a brain region associated with depression) was compared with one active (visual cortex stimulation) and one passive (sham stimulation) control group and found to generate significant reductions in depression scores. Depression scores were evaluated using widely accepted rating scales. Depression score reductions were significantly higher after DLPFC (40.4%) than after visual cortex (21.3%) or sham stimulation (10.4%). *DLPFC tDCS led to a significant quality of life improvement in depression patients, which outlasted the stimulation period for one month*. Further research regarding the use of tDCS for major depression is being conducted (19).
- A trial using tDCS was conducted in nineteen epileptic patients by Fregni et al. (20). Here, *cathodal* tDCS was applied to the field of interest (i.e. cortical

malformations causing refractory epileptic activity) in order to *decrease* cortical excitability. “Active compared with sham DC polarization was associated with a significant reduction in the number of epileptiform discharges” and the authors found that “the results suggest that this technique might have an antiepileptic effect based on clinical and electrophysiological criteria”. tDCS is further being evaluated for use in Epilepsy therapies.

2.2. tDCS Hardware

In order to apply tDCS to a patient, the following equipment is necessary:

- A certified medical DC stimulation device
- Batteries
- At least two tDCS-suitable electrodes and electrode holders or sponge pockets
- Tap water, normal saline solution or electrolyte gel
- Connection wires
- Rubber bands or a suitable head-gear for electrode attachment

2.2.1. The Direct Current Stimulation Device

A stimulation device must meet a number of special (safety) requirements to be suitable for medical or scientific use *on a human being.* For safety reasons not any DC generator may be used to apply weak direct current to the patient or subject. Only *battery driven* devices are suitable to be used for tDCS. This way it can be assured that there is no possibility of dangerously high voltages and/or currents being routed from the wall socket to the patient in case of defective stimulator electronics. Moreover, the maximum output current of the device should not be higher than a few mA, secured by a fuse. The device should allow adjustment of output current in fine increments (i.e. 0.1 or 0.25 mA steps). In order to prevent the operator from accidentally increasing current to values higher than desired, switches or buttons of the device should not allow too easy readjustment of the setup. Also, the device should indicate output current and voltage to the operator (but not to the patient) through clearly legible displays at all times. Apart from current magnitude, the operator also needs to have the opportunity to set the duration of stimulation. Stimulation duration is usually indicated to the operator by a countdown display.

For the protection and comfort of the patient, usually current does not just get switched on from zero to full magnitude at the beginning of stimulation, as it does not get switched

off from full magnitude to zero at the end of stimulation. There is a so called ‘fade-in’ or ‘ramp-up’-phase before stimulation and a ‘fade-out’ or ‘ramp-down’-phase after stimulation. Here, current is gradually increased to the desired magnitude and gradually decreased back to zero after stimulation. The fade-in and fade-out usually proceeds over a defined time interval (i.e. 30 seconds). Therefore, a tDCS device ideally offers adjustment of the duration of fade-in and –out phases.

In many scientific studies using tDCS, there is at least one active tDCS group of patients and at least one control tDCS group of patients. In the control group DC stimulation is not actually applied, but the patient is misled to believe he is being stimulated. This is called the ‘sham condition’ and is used to test if the effects of real tDCS are significantly stronger than possible placebo effects (21). Therefore it is very useful to researchers when a tDCS stimulator offers a ‘sham’ option. This means that after setting up the parameters for stimulation, a sham-switch may be activated. In this case current will only be ramped up for a short amount of time at each the beginning and the end of the regular tDCS session. This is to elicit normal tingling skin sensation in the fade-in and fade-out phases and is supposed to make the patient believe that he is actually being stimulated. In sham controlled studies, the device should always be placed in a way that does not let the patient see the control panel.

Furthermore, tDCS devices usually include an easily accessible stop-button which enables the operator to abort stimulation immediately in case of complications. Another useful option for tDCS devices is a button or sliding switch which allows a controlled temporary reduction of stimulation current in case of abnormally strong skin sensation or other adverse effects.

Figure 1: tDCS Devices

In order to enable the operator to optimize the stimulation setup, it is recommended that tDCS devices also include an impedance monitoring mechanism. Impedance of the setup depends mainly on the quality of electrode preparation (e.g. use of sufficient amount of saline or electrolyte gel, uniform contact between electrode and scalp, use of fresh electrodes). If impedance is too high due to bad electrode preparation, voltage demands for stimulation increase in order to hold the direct current magnitude. Impedance monitoring helps the operator prepare the setup in an ideal way and keep voltage demands reasonable to protect the patient and guarantee successful administration of tDCS.

It has to be noted that not only output current (and current density – see below) is a safety relevant parameter, but also the *output voltage applied to the patient* may play a role in patient safety and comfort during electrical stimulation (22-26). Current tDCS devices are limited to output voltages between 20 V and 43 V. This thesis and herein described experiments aim at reducing just this parameter, in order to facilitate even more protective DC stimulation.

For reasons of cost reduction and insufficient availability of proper tDCS devices, a significant number of clinicians and researchers use Iontophoresis-devices off-label for transcranial DC stimulation. Iontophoresis is a technology that uses direct current (usually ≤ 4mA) to deliver pharmaceuticals through the skin. Off-label use of Iontophoresis devices for tDCS is undesirable because such devices lack a number of control elements mentioned above and in addition they can reach excessively high output voltage levels, and thus are not built to deliver current to the brain.

2.2.2. Electrodes for tDCS

Two groups of electrodes (Figure 2) are currently being used for tDCS:

- Nonmetallic carbon rubber electrodes in combination with tap water- or saline-soaked sponge pockets
- Ag/AgCl electrodes in combination with electrolyte gel

The first group of electrodes is tDCS-standard and used in the vast majority of tDCS applications. These electrodes consist of a flexible conductive carbon rubber pad with a plug for the connection lead. For tDCS use, the carbon rubber pads are shielded with sponge pockets which will be moistened with tap water or a solution of normal 0.9%-concentrated saline prior to tDCS treatment. The saline solution is used to minimize the electrical impedance of the electrode-skin interface and reduce voltage demands for stimulation (23). Clinicians favor this non-metallic electrode solution because it seems to

almost completely disable the possibility of electrochemical reactions at the electrode-skin interface (27). Moreover, this is a low-priced solution for tDCS electrodes, which is favorable because for hygienic reasons tDCS electrodes should ideally be a one-time use product. These electrode-sponge combinations are mostly used in a size of 5x7cm, so they offer a fairly large contact area and thus a low current density at the electrode-skin interface. For this kind of electrode, usually rubber straps and plastic joints are used for attachment on the patient's head. There are efforts made by Soterix Medical Inc. to introduce a rather easy-to-use head-gear for flexible electrode attachment, which has been used in this study (Figure 7).

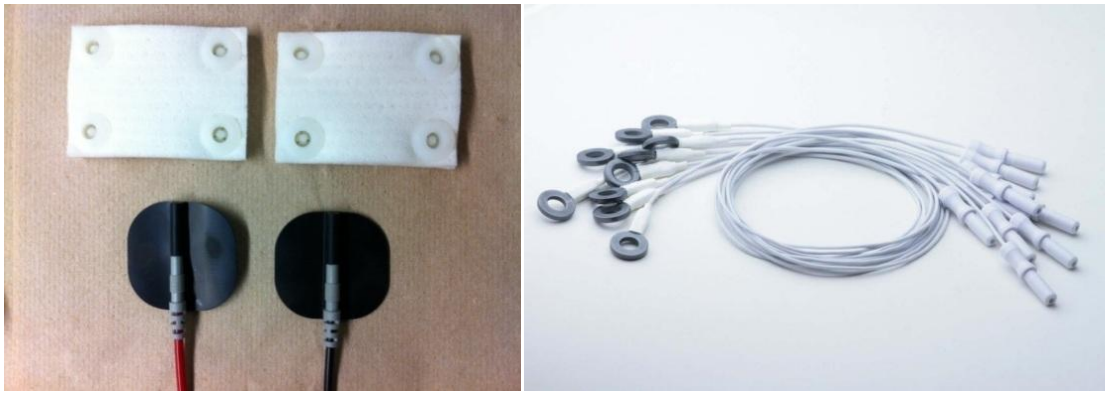

Figure 2: tDCS Electrodes; Left: Rubber Carbon Pads; Right: Ag/AgCl Ring Electrodes

As an alternative, Ag/AgCl electrodes have been introduced for use in tDCS, especially for an advanced technique called High-Definition tDCS which is currently being evaluated (28). Normally, this type of electrode is used in EEG applications for the recording of cortical electrical activity. Ag/AgCl electrodes consist of degradable metal (Ag) components and as a matter of principle support electrochemical reactions at the electrode-skin interface, which are driven by the applied stimulation voltage acting as a main power behind these reactions (22, 29). Minhas et al. were able to show optimized combinations of Ag/AgCl ring electrodes with conductive electrolyte gel, offering full support of DC stimulation (2mA x 22min) without abnormal pain perception or harmful or lasting skin reactions observed (29). Compared to carbon rubber / sponge electrodes, Ag/AgCl ring electrodes are significantly smaller in size (e.g. 12mm diameter) and thus result in higher current density (mA per cm^2; see below) being applied. This can lead to higher spatial focality of stimulation. Thus, a well defined small cortex area may be stimulated with higher precision than using large carbon rubber pads, leaving surrounding parts of the cortex unstimulated or stimulated with lower electrical intensity. Using this technology, *the region of interest may be targeted with higher precision*, leaving less uncertainty about effects through stimulation of undesired surrounding brain areas and *likely increasing the efficacy of tDCS* (30, 31). Moreover, a smaller size of electrodes

leaves more flexibility for positioning electrodes, especially when more than two electrodes are being used (a standard High Definition tDCS setup uses five electrodes).

2.3. Electrode Positioning for tDCS

According to the region of interest which is being targeted, electrodes need to be positioned in suitable ways for individual applications and studies of tDCS. In order to achieve reproducibility between studies and to prevent vagueness about electrode positioning, the International 10-20 system (Figure 3) is used to position (and describe) electrode montages. The International 10-20 system is the standard system for positioning EEG electrodes and is without reservations suitable for use in tDCS.

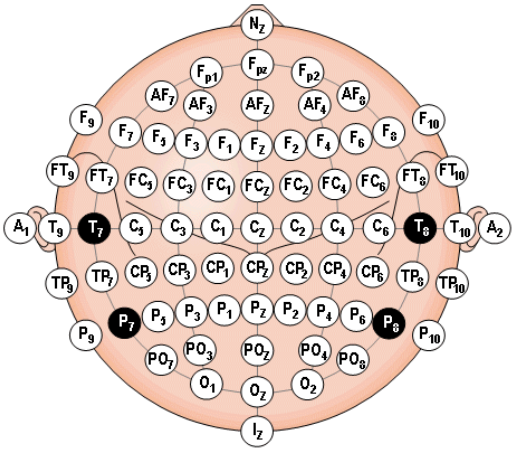

Figure 3: International 10-20 System

Often, electrode montages are named after 10-20 positions, e.g. 'C3-F4' with one electrode placed above C3 on the left hemisphere and one electrode placed over F4 over the right hemisphere. An alternative and more common approach is to name the electrode montage after the region of interest which is targeted. This could be for example 'M1-SO', where the stimulation electrode is placed over the primary motor cortex (M1) and the return electrode is placed superior to the contralateral orbit (SO). Other examples for this approach are DLPFC-SO (with the stimulation electrode placed over the Dorsolateral Prefrontal Cortex (DLPFC; left or right hemisphere) and the return electrode placed superior to the contralateral orbit (SO)) or OZ-Vertex (with the stimulation electrode placed over the occipital (Visual) lobe and the return electrode placed over the vertex). When electrode montages are not named after the 10-20 system, this system is still used to identify the correct positions on the scalp. In all cases it needs to be clarified which electrode is considered the stimulating electrode (anode or cathode) and which electrode plays the role of return electrode to complete the circuit. Of course *both electrodes are stimulating and have modulating effects on the underlying cortex* - the term 'stimulating electrode' is only regarded to the electrode which is stimulating *the field of interest*.

Electrode positioning for tDCS is a complex and critical aspect which directly influences clinical effects of stimulation (32). Nitsche stated in 2007 that "the efficacy of tDCS in eliciting excitability changes critically depends on the position of the reference electrode because of the interdependence between current flow direction and neuronal orientation" (33). Due to the critical role of the return electrode position and size it is often necessary

to experimentally find out optimal electrode setups (4, 32). Computer modeling studies play a helpful role in the development of optimal electrode setups, since they enable researchers to predict current distribution with high precision (30, 34, 35). Figure 4 shows two computer simulations of the distribution of electric field magnitude (V/m) for the montages M1-SO (C3-FP2 according to 10-20 system) and OZ-SO (OZ-FP2 according to 10-20 system).

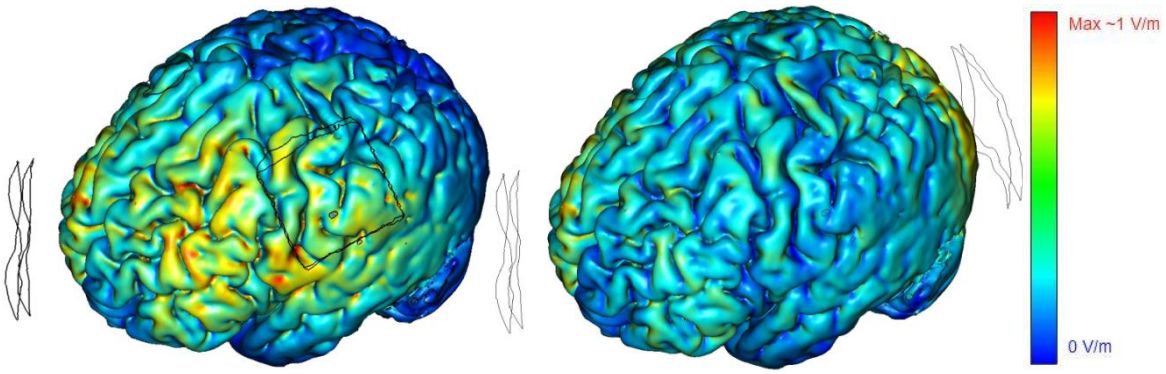

Figure 4: Computer Simulations of Electric Field Distribution in M1-SO and OZ-CZ Electrode Montages

2.4. The Electrode-Skin Interface, Voltage and Impedance During tDCS

The electrode-skin interface consists of the electrode (including sponge pads), agents for conductance increase (saline solution, tap water or electrolyte gel) and the underlying skin. This interface plays an important role, as current passes from the external stimulation equipment into the human body and exits it through this interface, and it contributes significantly to the *characteristic impedance in tDCS setups*. It is well known that human skin has dynamic electrical characteristics. *The electrical impedance of human skin in vivo changes when electrical current is applied, generally with a downward tendency*. This is effective in case of direct current as well as alternating current. Skin impedance is dependent on frequency and, more importantly in case of DC stimulation (where ω=0), *on current magnitude, density and duration (36-38)*. It should be noted here as a bottom line that *in general the electrical impedance of human skin is expected to decrease when current is applied and further decrease when current magnitude or density are increased and when current flow proceeds over time.*

Depending on the used type of electrode, the electrode may also contribute to the dynamic impedance of the interface. Electrodes certainly contribute to the total

impedance level of the whole interface, as different electrode types have different impedance levels, according to used materials. For example metal electrodes are expected to have lower impedance than carbon rubber electrodes.

The electrode-skin interface is for above mentioned reasons considered to be the main contributor to the *dynamic* impedance of the entire stimulation setup. The components contributing to the *entire* impedance of the stimulation setup are:

- The stimulator device and its internal resistance
- The connection leads and their electrical resistance
- The electrodes
- Skin (scalp)
- Skull
- Cerebrospinal Fluid (CSF)
- White and grey matter
- Blood and blood vessels

The stimulator device may be considered to have relatively stable internal resistance. Resistance of the connection leads may be neglected. The heterogeneous mixture of skull, CSF, white & grey matter and blood vessels certainly contributes significantly to the overall impedance level, though is not considered to play a major role in the *dynamic* part of impedance.

The dynamic nature of electrical impedance in tDCS setups will be examined quantitatively and qualitatively in the experimental part of this work.

During tDCS, electrical current is the main predetermined electrical parameter, as tDCS is carried out in a strictly current controlled manner. As specified by Ohm's law, current (I) is defined by the quotient of voltage (V) and impedance (R).

$$\boldsymbol{I} = \frac{\boldsymbol{V}}{\boldsymbol{R}} \qquad \text{(Equation 1)}$$

With current being held constant during the course of DC stimulation and impedance expected to be dynamic over time, voltage demands will be dynamic as well in order to maintain constant current. Due to the relation in Equation 1, voltage demands are expected to increase when overall impedance increases, as they are expected to decrease when overall impedance decreases.

The important role of the electrode-skin interface is not only due to its contribution to the dynamic impedance but also to the fact that it is the site of possible electrochemical

reactions (22) and painful skin sensations taking place. Even though the commonly used types of electrodes and saline/electrolyte gels are generally found safe and well tolerated for use in tDCS, there is a possibility of incidents like irreversible harmful electrochemical reactions and more than moderate pain perception or even skin injuries at the electrode sites (see below). For example using Ag/AgCl electrodes, voltage driven processes like AgCl formation at the anode and AgCl depletion at the cathode take place. These processes are reversible faradaic reactions, but may be followed by irreversible faradaic reactions when the applied potential difference (voltage) is too high or when AgCl or Cl in the electrodes are depleted. In this case it is possible that an irreversible migration of electrochemical products into the skin and underlying tissues happens which is undesired and harmful (22, 29). For this reason, the use of Ag/AgCl or other metal electrodes for DC stimulation is critical to some extent because operators *have to prevent excessive reuse of such electrodes*.

Using carbon rubber pads and saline soaked sponge pockets, the above described electrochemical processes are not supported. Though, the exact physical processes happening with the use of DC and these electrodes are not entirely known, and the magnitude of applied electrical potential may be a harmful force in this case as well. For example, Ion migration from the applied saline solution into the skin is rather voltage driven than current driven, and could play a role in pain perception, as a relation between NaCl concentration and skin sensation has been observed (23). Another important factor is heterogeneous current distribution (see below) through electrodes and sponges which can lead to increased local current density and voltage, possibly co-inducing skin sensation and injury. As described below, these standard electrodes have been involved in voltage/impedance related skin injuries in several cases.

These facts and theories support the notion that *a generally reduced voltage level and lower peak voltages during tDCS may increase patient safety and comfort* and were a central motive for experiments leading to reduced voltage stimulators and Limited Total Energy (LTE) tDCS.

2.5. Safety Aspects in tDCS

2.5.1. Safety Parameters

With rising interest in tDCS as a tool for cognitive and therapeutic studies, strong efforts have been made to determine relevant parameters and thresholds for safe application of tDCS in humans. To this day though, no tDCS study or single case is known where *neural* injury (i.e. a brain lesion) has been caused and all currently and in the past applied tDCS paradigms can be considered safe from this point of view. The interest in robust safety parameters and thresholds is closely connected to *ambitions of increasing stimulation intensity, duration and repetition rate as these steps are expected to strengthen the therapeutic effects of tDCS.*

Previous studies regarding current distribution through scalp electrodes and electrical parameters and thresholds for neural injury in animals build the foundation for safety conclusions made by tDCS researchers. Animal studies in the 1980s investigated parameters which contribute to neural injury (i.e. brain lesions) during electrical stimulation both invasively and non-invasively and using different current waveforms (pulsed currents) (39-41). These studies were not designed to investigate noninvasive DC stimulation and thus conclusions cannot be transferred to tDCS use without special caution. However, as summarized by Nitsche (42), it has been found that the following parameters seem to have great influence on whether electrical stimulation causes damage to neural tissue or not:

Current Density (mA/cm^2): Stimulation Strength (mA) / Electrode Size (cm^2)

Total Charge (C/cm^2): [Stimulation Strength (mA) / Electrode Size (cm^2)] x Pulse Duration x No. of pulses

Charge per Phase (µC): Stimulation Strength (A) x Duration of a single pulse (µs)

Charge Density (C/cm^2): [Stimulation Strength (mA) / Electrode Size (cm^2)] x Duration of a single pulse

Charge per phase is a parameter not applicable to tDCS, as it describes delivered charge in periodical and/or pulsed waveforms. Charge density and total charge can be considered equivalent in tDCS, *where only one very long pulse is delivered*. Charge density and total charge designate *the amount of charge which is being transported through every cm^2 of the electrode-skin-interface area* over the entire stimulation protocol – hence these parameters increase linearly with proceeding stimulation duration.

The main parameter regarded to determine possible neural injury in noninvasive DC stimulation, is current density (mA/cm^2). Current density is generally defined as the quotient of current magnitude and electrode size. It is important to take into consideration that *nominal current density and actual local current density can differ significantly*, due to effects of inhomogeneous current distribution:

As first described by Rush and Driscoll, current distribution across the head is strongly heterogeneous (43). The amount of current that reaches the brain through scalp and skull is only a fraction of the total current, while a large fraction of the applied current is *shunted through the scalp without entering the brain* (35, 43). This allows the conclusion that the general level of current density delivered to the brain is possibly smaller than the nominal level of current density at the electrode-skin interface. However, *it cannot be ruled out, that conductive channels in the strongly heterogeneous brain tissue cause local spots of increased current density*. At the electrode-skin interface, current density is known to be non-uniform as well, due to increased current density at the electrode edges (34, 44). This may be especially meaningful for the occurrence of local pain, skin sensation and skin injury during tDCS (see below) and accounts for extra careful electrode preparation and assembly with uniform contact between electrodes and skin.

Current distribution can be estimated in helpful computer-modeling studies, but not in real time during tDCS (30, 34, 35, 44). To this day though, clinicians have no choice but to rely on nominal current density as a way of quantifying DC stimulation intensity. *As a bottom line it should be noted, that when nominal current density is specified for a stimulation paradigm, it cannot be ruled out that higher actual current densities occur in the same paradigm, and that careful electrode preparation, assuring uniform contact, is one measure to minimize such effects.*

Thresholds for neural injury caused by cathodal tDCS have been investigated in rat experiments by Liebetanz et al. in 2009 (45). In this study, a *small stimulating electrode* was directly fixed on the cranium, with a *large return electrode* mounted on the rats' chests. Thus is could be assumed that in this case nominal and actual current densities were almost analog, which allowed determination of thresholds for the occurrence of brain lesions:

- 10 minutes cathodal stimulation with a *nominal current density of 142.9 A/m^2 (= 14.29 mA/cm^2)*
- This is corresponding to a *nominal charge density of 52400 C/m^2 (= 5.24 C/cm^2)*

The *size of brain lesions increased linearly with charge density* in these experiments, which is a strong indication for the safety importance of this parameter.

However, as summarized by Liebetanz et al., the thresholds determined in these animal experiments are "*two orders of magnitude higher than the charge density currently applied in humans*" and "*although these results cannot be directly transferred to humans …. encourage the development of intensified tDCS protocols*" (45).

2.5.2. Skin Lesions in tDCS

In two recent tDCS studies, eight cases of skin injuries caused by repeated DC stimulation have been reported. In three cases, skin lesions occurred at the site of the anode (25), while in five cases lesions were observed at the side of the cathode (26). Skin lesions are documented in Figure 5. In all cases, lesions appeared after multiple repeated and prolonged stimulation sessions, and there were no subjects involved having any known skin conditions or hypersensitivities.

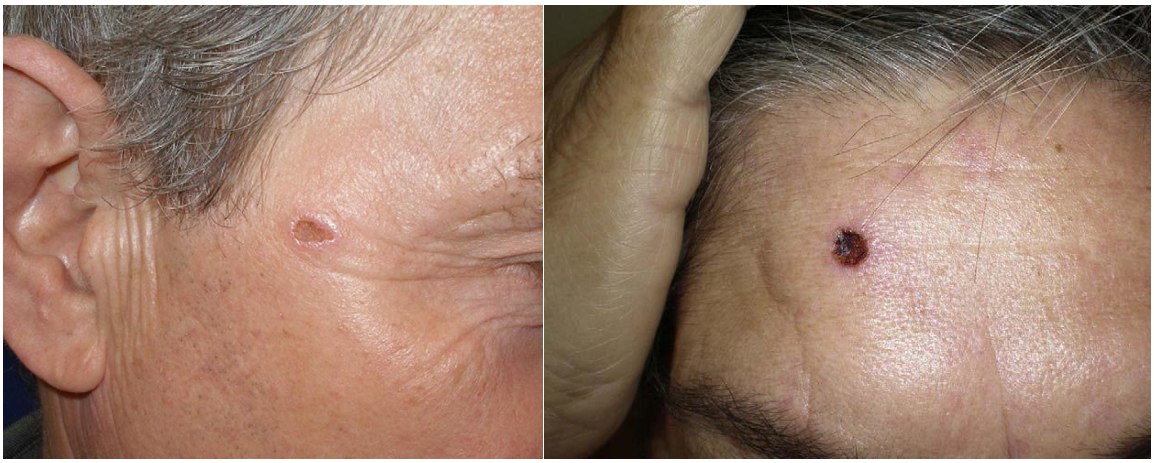

Figure 5: tDCS Skin Lesions; Left: Frank et al.; Right: Palm et al.

Cathodal skin lesions as reported by Palm et al. appeared in five subjects, each after four or five daily tDCS sessions of 2 mA over 20 minutes. The authors observed that *lesion size was proportional to skin impedance, with higher skin impedance related to larger skin lesions.*

Anodal skin lesions as reported by Frank et al. appeared in three subjects after each three sessions (two per week) of 1.5 mA tDCS over 30 minutes. The same electrodes and sponges have been used in all three cases.

In all cases, 35 cm^2 large sponges were moistened *with tap water*. Compared to saline solution, tap water is associated with a higher impedance level, subsequently leading to higher voltage being applied.

This and the observed correlation between impedance and lesion size lead to the presumption, that skin injuries after direct current stimulation are co-induced by high impedance and voltage.

Moreover, skin injuries apparently occur due to intensive repeated DC polarization, which brings up the question which repetition rate and dosage of tDCS can be applied safely.

Other possible factors contributing to these incidents are:

- Non-uniform current distribution at the electrode-skin interface, leading to increased local current density (34, 44)
- Local accumulation of chemical substances in the sponges, due to inadequate re-use, rinsing and disinfection of sponges, amplify effects of non-uniform current density (25)
- Impedance related temperature increases, though rather unlikely as described by Datta, Elwassif and Bikson (46)

However, the reports of skin injuries call for increased awareness of patient safety and particularly suggest the *optimization of electrode preparation and stimulation protocols in order to avoid similar cases in the future*. This was a central motivation for the study aiming to develop reduced voltage stimulation, which is described in the experimental part of this study.

3.Experimental Part

3.1. Foreword

In the time from June to August 2011, a short experimental study aiming at a reduction of the maximum output voltage of tDCS stimulators has been conducted. This study was conducted in the Neural Engineering Laboratory of the City College of New York in close collaboration with Soterix Medical Inc. All experiments conducted in this study were approved by the Institutional Review Board of the City College of New York and all participants of the study gave written informed consent before participating in the experiments. This experimental study is part of a continuous enhancement process of the Soterix tDCS stimulation devices. Device modifications deducted from this study will be implemented into the Soterix 1x1 tDCS stimulator, which is the basic tDCS device in the Soterix product portfolio, in 2012.

3.2. Goals of this Study

As mentioned above, the main goal of this study was to *investigate how far the maximum output voltage of the stimulator device could be reduced, still guaranteeing to allow successful DC stimulation using a range of usual conditions.* This aims at being an additional safety and comfort factor in tDCS, especially preventing skin injuries as reported by Palm et al. and Frank et al. Moreover, an output voltage reduction appears reasonable considering that *tDCS protocols will likely be intensified in the future*, with current magnitude being increased. This will lead to higher voltage demands as well – thus without voltage reduction techniques, much higher voltages will be applied in the future (e.g. when tDCS protocols using 4-5 mA stimulation current will be introduced in a few years).

Another motivation of this study was initiated by clinical collaborators who (by personal communication) reported cases where stimulator devices independently conducted an abortion of stimulation. In such cases, abnormally high impedance was reported, possibly due to inadequate electrode preparation. This led to situations where the tDCS device could not gain or maintain the target current while voltage increased to maximum level. In this kind of situation, tDCS stimulators repeatedly aborted stimulation *without leaving the operator a chance to refine the (electrode) setup in order to carry out a successful stimulation session*. This is especially problematic as it leads to reproducibility problems as well as a disturbance of the clinical work flow (especially in large scale clinical trials)

and in case of a necessary repetition of stimulation is an inconvenience to the patient. Therefore, *this study did not only aim at a reduction of output voltage, but also at introducing a new and more robust and intelligent stimulation protocol which prevents the described troublesome cases of stimulation abortion.*

3.3. Experimental Part: Methods

3.3.1. Data Recording

In order to collect meaningful data to answer the preliminary asked questions and to meet ethical and safety guidelines, caution was advised when designing the experiments of this study. Since this study aimed at an output voltage reduction, voltage, current and impedance data was recorded in tDCS sessions. Given a constant current, it appeared adequate to record voltage and current and use that data to calculate impedance values according to Equation 1. The recording of impedance in tDCS setups with normal digital multimeters, especially using saline soaked sponges and carbon rubber electrode pads, is known to be problematic. Multimeters tend to measure unreasonably high impedance values or even indicate an overload in this kind of setup. This is most likely due to too small measurement currents injected by the multimeter (15µA, Fluke 117 Digital Multimeter), which cannot overcome polarization barriers at the electrode-skin interface. This also led to the decision to measure current and voltage during stimulation experiments and to calculate the impedance across electrodes using the collected data, with the applied current and voltage being high enough to provide precise impedance data. In the experiments, multimeters from Fluke Corp. (Fluke 117 Digital Multimeter) and Circuit Specialist Inc. (Circuit Specialist MY68 Multimeter) have been used.

In order to generate a complete impedance profile of tDCS stimulation setups, impedance measurements were not only made during stimulation, but also prior to and after stimulation. As described above, the impedance across electrodes was expected to be *current dependent*. To investigate this dependency in detail, impedance measurements prior to and after stimulation were carried out using three different test current magnitudes. Measurements were carried out systematically in the following order:

One minute prior to stimulation, impedance was measured by injecting 50 µA and shortly afterwards 100 µA through the already assembled electrodes and recording the compliance voltage of these test currents. Directly after those measurements, electrodes have been connected to the prototype tDCS stimulator (see below) and offset current and compliance voltage have been noted.

One minute after stimulation, the remaining offset current and compliance voltage of the prototype tDCS stimulator, which was still connected to the electrodes, have been noted. Shortly afterwards, measurement currents of 100 µA and 50 µA were injected through the electrodes and compliance voltages were recorded.

Measurement currents were injected using a separate direct current stimulator which allows precise adjustment of current (µA) and indicates the applied stimulation current and voltage through built-in displays (CX 6650, Schneider Electronics, Gleichen, Germany).

This way, three impedance values each prior to and after stimulation have been recorded. During direct current stimulation, three multimeters have been connected to the tDCS setup:

- One multimeter in series with the electrodes and prototype stimulator, measuring the applied stimulation current
- One multimeter parallel to the electrodes and prototype stimulator output, measuring the voltage drop across the subjects head
- One multimeter parallel to the power transformer of the prototype stimulator, measuring the (load dependent) momentary maximum output voltage of the stimulator

The maximum momentary output voltage of the stimulator is the highest voltage which the stimulator can output. This value varied slightly from case to case and over time, depending on the load of the stimulator, and was thus monitored.

One conventional option for data recording was to connect the entire setup to a digital PC-based data recording solution (e.g. Signal or LabView). Such a setup was avoided in this study in order to keep the experiments and the technical setup simple. Moreover, the time accuracy of such a measurement solution has been found unnecessary for these experiments, where the course of voltage and impedance *over minutes* were investigated. Millisecond-accurate data was not considered necessary to make meaningful conclusions from this study. Instead, data was recorded using a digital video camera pointed at the displays of the three multimeters during the entire stimulation session. This way, continuous data would be available for possible cases where detailed analysis of the chronological data would be necessary. For general data analysis, it has been decided that 10 second intervals between data points would be sufficiently short to allow calculation of impedance profiles which would provide enough detail for the purpose of this study.

As an addition, subjects have been asked several times in each experiment to rate their currently perceived skin sensation. This is called the ‘pain rating’. The pain rating was adapted from several other studies, like Minhas et al. 2010. A visual analog pain scale (Figure 6) was presented to the subjects in order to help rank the perceived pain on a scale from 0 – 10, with 0 being no sensation and 10 being agonizing pain.

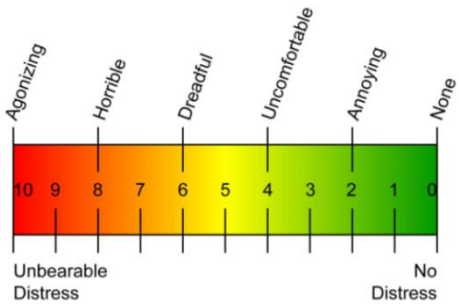

Figure 6: Visual Analog Pain Scale

3.3.2. Electrode Montage

Where to place the electrodes in the experiments was the next central element of experimental design. Since this was not a study where physiological, behavioral, motor or any other medical effects of tDCS were investigated, it initially remained uncertain if application of DC stimulation to the brain could be justified in these experiments. In former studies like the investigation of electrode tolerability by Minhas et al. in 2010, experiments were conducted with DC stimulation on subjects’ forearms to avoid actual brain stimulation (29). It seemed problematic that from experience and pilot experiments it was known that impedance of forearm-skin and impedance of scalp (also with hair playing a role in tDCS impedance) are not necessarily equivalent and there was the possibility that *data recorded in forearm experiments would not be transferable to realistic tDCS setups*. The worst case scenario would be a newly developed low-voltage stimulation protocol based on forearm impedance data that does not provide target current in a realistic tDCS setup. Thus it was decided that experiments should be conducted *using a realistic electrode configuration on subjects heads*. Since preliminary experiments in the neural engineering lab at CCNY and dozens of studies all over the world had been conducted applying tDCS without adverse effects observed, the Institutional Review Board of CCNY approved this kind of experiment for the study.

Being clear that in this study subjects would receive actual brain stimulation, further questions arose regarding safety and stimulation setup. Still, a realistic experimental design that would lead to significant conclusions was sought. The main goal was now to find a setup and protocol that would not lead to any effects on well-being, behavior, motor function or limitation of body functions, like modulation of vital parameters. The only cases where adverse effects of direct current stimulation on vital parameters have been reported involved the use of an extracephalic reference electrode (placed on a location *distant* from the head) (47, 48). This kind of setup possibly enables current flow through autonomic centres of the brainstem, which control heart rate, respiratory frequency, blood

pressure etc. In the reported case, “an episode of transient respiratory depression in a healthy volunteer under frontal tDCS with an extracephalic reference electrode suggested that this electrode montage could lead to a modulation of the brainstem respiratory centre” (49). Even though in 2010 Vandermeeren was able to show systematically that application of tDCS to healthy subjects with an extracephalic electrode can be considered safe (49), it has been decided that such an electrode montage would be no option for this study. This also means that the conclusions and hardware developments made in this study cannot be applied without modification to tDCS setups where an extracephalic return electrode is used. Since the general impedance level in a tDCS setup significantly depends on the distance between electrodes, such an extracephalic montage would lead to a higher impedance level than any montages placing the return electrode on the head, closer to the stimulating electrode. Hence, it also seemed reasonable to choose an electrode montage without extracephalic reference electrode because that would rather lead to low impedance across electrodes and thus *favor the development of a reduced voltage tDCS design*. Moreover, in the vast majority of clinical tDCS studies such electrode montages are being utilized, while extracephalic electrode montages remain uncommon.

An overview of tDCS studies performed in humans since 1998 (27) revealed that in the vast majority of studies, variations of the M1-SO electrode montage with the stimulating electrode placed over the primary motor cortex and the return electrode placed superior to the contralateral orbit (= over the opposing forehead) were used. Parameters like stimulation polarity, stimulation duration, applied current magnitude and density varied widely across the summarized studies. Effects of motor cortex stimulation also varied widely across studies according to polarity etc. and according to which behavioral, physiological or pharmacological effects were investigated in each study. 55 studies are named in this review where the primary motor cortex has been stimulated, primarily the hand-associated area of the motor cortex. In almost none of the summarized studies any other adverse effects on well-being or health but tingling or itching skin sensation at the electrode sites have been observed. In three studies, light flashes have been reported by subjects at the moment when current was switched on or off (50-52). This is possibly due to inadequate fade-in and fade-out current waveforms used in those studies. In another study, one subject reported mild headache after motor cortex tDCS (21).

Compared with motor cortex stimulation, other montages were found less often. Apart from M1 tDCS, stimulation of the dorsolateral prefrontal cortex (DLPFC, right or left hemisphere) was the most common approach in the summarized studies, with 17 studies investigating DLPFC tDCS. In four of the DLPFC studies, side effects like discomfort,

headache and mood changes have been described (17, 18, 53, 54). This is very likely not due to the stimulation setup, but rather because of subjects who participated in these studies – e.g. patients suffering from major depression, fibromyalgia and alcoholism.

Another review of tDCS studies by Poreisz et al. in 2007 analyzed 567 tDCS sessions with the conclusion, that “tDCS applied to motor and non-motor areas according to the present tDCS safety guidelines, is associated with relatively minor adverse effects in healthy humans and patients with varying neurological disorders” (55). Here again, mild tingling sensation was reported to be the most frequent adverse effect (70.6% of the subjects), while moderate fatigue (35.3%), headache (11.8%), nausea (2.9%) and insomnia (0.98%) where reported less often. In the analyzed studies, 75.5% of the subjects were healthy patients, while migraine patients (8.8%), post-stroke patients (5.9%) and tinnitus patients (9.8%) summed up the rest of the subject group. This review of a high number of tDCS sessions left no indication that a tDCS study in healthy subjects could possibly cause safety concerns when conducted according to present tDCS safety guidelines.

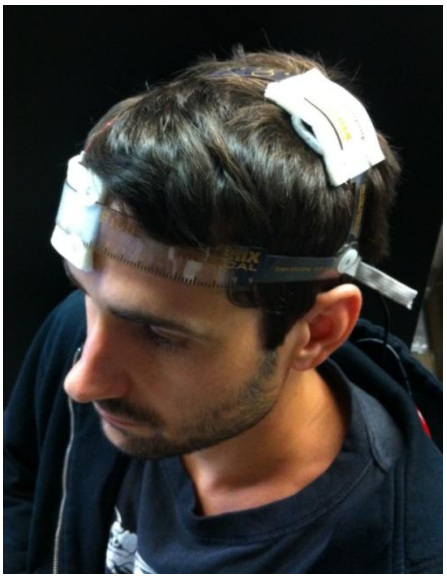

Figure 7: M1-SO Electrode Montage Used in this Study

After analysis of previous studies it seemed reasonable to choose *the most common electrode montage* for this study as it would help maximize impact and usability of a newly developed tDCS stimulator design. *Stimulation of the left motor cortex with a reference electrode above the contralateral orbit (M1-SO) was administered in this study (*Figure 7*).*Also after analysis of review articles, from the safety point of view, motor cortex stimulation appeared to be the obvious choice for this study. The electrode montages for DLPFC stimulation do not differ significantly from M1-tDCS montages regarding electrode location and distance. Differences in impedance and in voltage demands between such montages are thus not to be expected. Hence, there was no indication that a new stimulation protocol suggested by this study using a M1-SO electrode montage could not easily be used in a DLPFC-SO or similar electrode montage (e.g. OZ-CZ with the stimulating electrode placed over the visual cortex and the return electrode placed over the vertex) *without modification*.

3.3.3. Electrode Preparation

Special care has been taken of electrode preparation, as this was expected to be a key factor for successful completion of this study. Loo et al. already pointed out the importance of careful inspection of the skin and preparation and attachment of electrodes, especially the role of uniform skin contact and sufficient saline use (56). Carbon rubber pads (Model CARB5010; www.emsandtens.com) and sponge pockets (Soterix Medical Inc.; 5x7cm) were used in this study. As described above, this is the most common electrode solution for tDCS and thus a reasonable choice to maximize impact and realistic experimental design of this study. Prior to every experiment, the carbon rubber pads were assembled to the connection leads and then placed in the sponge pockets. Now, each electrode/sponge combination was moistened with approximately 10 ml of normal 0.9% concentrated saline solution (B.Braun, Melsungen, Germany) with a pipette. 0.9% concentration of saline corresponds to 154mMol/l. This is a slightly higher saline concentration than suggested by Dundas et al. in 2007, who recommended the use of saline between 15 and 140 mMol/l due to reduced skin sensation observed when using lower concentrated saline (23). On the other hand, a lower saline concentration also leads to lower electrical conductivity of the solution and thus higher voltage needed to gain and maintain target current. Very contrary to Dundas et al., Loo et al. (56) reported that “adding saline usually reduces any pain experienced”. Though, the study by Dundas et al. is the only investigation systematically looking at the correlation between saline (concentration) and pain perception.

However, the reports of reduced skin sensation with lower saline concentration are also opposed by the notion by Lang et al. that skin sensation during DC stimulation correlates to magnitude of the applied voltage (24). Moreover, in the vast majority of tDCS studies using saline solution for electrode moistening, it has not been specified which saline concentration was used. It appears reasonable to assume that in most cases normal 0.9% concentrated saline was used, since this a *widely used product which is immediately available almost everywhere in clinical environments*. This was another motivation to use normal saline in the upcoming experiments, since this would be an electrode setup most realistic and alike tDCS in clinical use.

After electrodes and sponges were moistened with saline solution, they were placed carefully on the head on the M1-SO positions as defined by the 10-20 system and held in place by a tDCS head-gear (Soterix Medical Inc., Figure 7: M1-SO Electrode Montage Used in this Study). The operator applied soft pressure and massage-like motions to the electrodes in order to establish adequate uniform contact and wetting of the underlying

hair and scalp region. *As observed in pilot experiments using real time impedance monitoring, this reduces initial impedance of the electrode/hair/scalp-interface significantly*. However, 10 ml is a fairly large amount of fluid for 5x7cm sponges, and in very few cases of excessive wetting and dripping (subjects with very short hair) fluid needed to be sponged up using a regular paper towel. Stimulation was not started unless impedance across electrodes was < 50 kΩ (I = 50 µA). In very few cases, additional saline had to be used to further moisten the sponges in order to decrease impedance to values < 50 kΩ.

In between experiments, extra care has been taken to very thoroughly rinse the sponges and clean the electrodes with large amounts of water. This was of major importance, as no significant amount of saline should remain in the sponges. If sponges dried out with rests of sodium chloride remaining inside, the saline concentration could cumulatively increase with every experiment where new saline solution would be used to moisten the sponges. On one hand, this could lead to a continuous decrease in sponge impedance with every new experiment; on the other hand this would continuously increase saline concentration in the sponges to values much higher than the desired 154mMol/l and possibly amplify skin sensation and non-uniform current distribution (44). In order to avoid this, sponges have been rinsed under floating water for several minutes after each experiment to rinse out all saline. Over the course of the study (18 experiments in three weeks), three pairs of electrodes and sponges have been used, with a total of six uses per pair. It is noteworthy that in a clinical environment, for hygienic reasons, sponges and ideally also carbon rubber pads should be used only as one-time-use products. Ideally, the above described possible complications would not emerge in clinical use.

3.3.4. Stimulation Parameters

In order to investigate the correlation between current and impedance, experiments with two different current magnitudes were carried out. Subjects were stimulated with 1.5 mA and 2.5 mA in separate experiments. 2.5 mA is at the top end of current magnitudes used in tDCS and was chosen to investigate feasibility of this paradigm for an upcoming multi-center tDCS-trial in major depression. As described here, *all currently valid tDCS safety limits were complied*. Given the 35cm^2 surface area of the applied electrodes, nominal current densities of 0.0429 mA/cm^2 (I = 1.5 mA) and 0.0714 mA/cm^2 (I = 2.5 mA) were reached in the experiments. These values are far below the above mentioned threshold for neural injury investigated by Liebetanz (= 14.29 mA/cm^2). In all experiments, stimulation was delivered for five consecutive minutes with a linear fade-in and fade-out phase of each 30 seconds. Including the fade-in and fade-out phases, this sums up to

delivered charge densities of 0.0141 C/cm^2 (I = 1.5 mA) and 0.0236 C/cm^2 (I = 2.5 mA), also orders of magnitudes smaller than Liebetanz' threshold (= 5.24 C/cm^2). All safety relevant parameters in this study were significantly smaller than those successfully used in a pilot study investigating safety and efficacy of HD-tDCS (28). Here, 2 mA were delivered over 20 minutes through approximately 1 cm^2 large ring electrodes. This corresponds to a current density of 2 mA/cm^2 and charge density of 2.4 C/cm^2 successfully applied at the stimulation electrode in 13 healthy subjects without adverse effects observed.

From the above described calculations it was concluded, that the stimulation parameters used in this study are not only compliant to current safety guidelines, but also fall far below previously successfully applied higher stimulation intensities. The entire stimulation protocol applied in this study was hence considered absolutely safe for human subjects.

In order to rule out any possible (though extremely unlikely) effects of stimulation polarity on impedance and also to increase sample size with a very limited number of subjects available, each subject participated in two experiments with the same stimulation intensity but interchanged polarity. This resulted in four experiments per subject: 1.5 mA anodal M1 tDCS; 2.5 mA cathodal M1 tDCS; 2.5 mA anodal M1 tDCS; 2.5 mA cathodal M1 tDCS.

Voltage limits were determined in pilot experiments and set at 14.5 V (1.5 mA) and 18.5 V (2.5mA). All stimulation parameters are summarized in Table 1.

	1.5 mA Experiments	**2.5 mA Experiments**
Current Magnitude	1.5 mA	2.5 mA
Electrode Area	35 cm^2	
Current Density	0.0429 mA/cm^2	0.0714 mA/cm^2
Charge Density	0.0141 C/cm^2	0.0236 C/cm^2
Polarity	Anodal M1 and Cathodal M1	
Stimulation Duration	5 minutes	
Ramp Duration	30 s linear ramp-up and ramp-down	
Output Voltage	Max. 14.5 V	Max. 18.5 V
Electrode Montage	M1 – SO	

Table 1: Stimulation Parameters

3.3.5. The Prototype tDCS Device

The DC stimulator used in this study had to meet special requirements, as experiments should be carried out with a reduced voltage limit from the very start. Moreover, the voltage limit should be adjustable and when reaching the maximum output voltage, the stimulator was supposed to continue stimulation, even at reduced stimulation current.

According to these aspects, the central design inputs for the development of the stimulator were:

- Current magnitude adjustable from 0-3 mA
- Maximum output voltage adjustable from 10-30 V
- Current controlled
- A fully automated fade-in and fade-out mechanism, starting a linear 30 second long current ramp at the push of a button
- The device should continue stimulation when maximum voltage is reached and the target current is not reached
- Battery driven

The prototype device (Figure 8) was developed by engineers at Soterix Medical. In the end, the delivered prototype stimulator fulfilled all central functional demands, and enabled full realization of the experiments as they were planned.

Certain limitations in usability like a distinct load-dependency when adjusting current and output voltage will be eliminated when implementations into the Soterix 1x1 tDCS device are made.

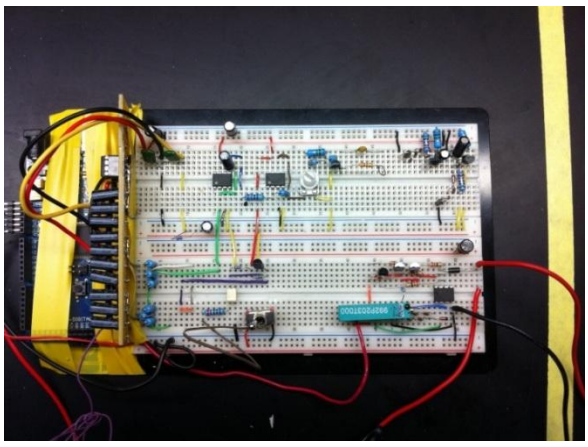

Figure 8: Prototype tDCS Device

3.3.6. Human Subjects

Six healthy adult subjects participated in this study. Three subjects participated in both the 1.5 mA and 2.5 mA experiments, resulting in four stimulation sessions which each of these subjects received. One other subject only participated in the 2.5 mA experiments, while the last two subjects only participated in the 1.5 mA experiments, resulting in a total of two stimulation sessions which each of these three subjects received. Subject assignment happened solely due to day-to-day availability for the experiments.

All subjects were informed about possible side effects and gave written informed consent before participating in the study. Moreover, all subjects who participated in this study were colleagues from the neural engineering lab at CCNY or from Soterix Medical Inc. and thus were already well educated about tDCS and theoretical side effects. Subjects were informed that they could withdraw from the study at any time or that single experiments could be aborted at any time without justification necessary. Subjects participated in no more than one experiment per day, leaving at least 24 hours between experiments. Prior to each follow-up and after the last experiment, subjects were interviewed about side effects they may have observed after finishing the previous experiment.

3.3.7. Data Analysis

All data analysis was performed using Microsoft Excel. After completion of each experiment, all data was entered into spreadsheets. Data was taken from notes made in the experiment and from video recordings described above.

Data was systematically organized in one spreadsheet for all 1.5 mA experiments and another one for all 2.5 mA experiments. Current magnitude, applied voltage and momentary maximum output voltage were noted in 10 second intervals and inserted into the spreadsheets, resulting in 41 data points (10 seconds prior to tDCS; 30 seconds fade-in; 300 seconds stimulation; 30 seconds fade-out; 30 seconds post tDCS).

For each data point, voltage and current values were averaged, with n=8 for 2.5 mA and n=10 for 1.5 mA experiments. Using these average values, average impedance has been calculated for each data point according to Equation 1. This way, average impedance profiles for the 1.5 mA experiments and the 2.5 mA experiments were generated.

Given the assumption that all voltage values at each data point are normally distributed (n=8 for each of the 41 2.5 mA data points; n=10 for each of the 41 1.5 mA data points), the top 99^{th} percentile voltage interval for each data point has been calculated using the

Excel function ‘NORM.INV’. In order to do this, the standard deviation of voltage values had to be calculated first for each data point with the Excel function ‘STDEV.P’.

The top 99th percentile of voltage values indicates a voltage threshold at each data point that is expected to not be exceeded in 99% of the cases. This appeared to be a suitable statistical tool to reliably *predict universal maximum voltage demands.*

Average voltage, averaged impedance, top 99th percent voltage intervals and stimulation current have been plotted over time in several figures for 1.5 mA experiments and for 2.5 mA experiments.

The course of voltage has also been plotted separately according to stimulation polarity. For the 1.5 mA experiments this resulted in n=5 for cathodal experiments and n=5 for anodal experiments. For the 2.5 mA experiments this resulted in n=4 for cathodal experiments and n=4 for anodal experiments. Graphs have been compared and not found to differ significantly, thus it has been decided to not further investigate aspects regarding stimulation polarity.

The impedance values measured prior to and after stimulation have been grouped by measurement current (50-100-150/200µA), stimulation current (1.5/2.5mA) and chronologically (prior to / after tDCS). The third used measurement current (150/200µA) differed between the 1.5/2.5mA experiments. This is the offset current of the prototype stimulator used in this study. The offset current of the stimulator was target current dependent and was 150µA in the 1.5mA experiments and 200µA in the 2.5mA experiments.

Student’s t-tests were used to investigate if impedance value groups differed significantly depending on the three above mentioned criteria test-current, tDCS-current and chronology. Since in some cases of the comparisons sample sizes were unequal (i.e. when comparing 1.5mA experiments with *n=10* to 2.5mA experiments with *n=8*), two-sided *unpaired* t-tests were used in all cases to maintain simplicity. Unpaired t-tests are less powerful compared to paired t-tests with equal sample sizes, but there was no indication that they could not generate sufficiently meaningful results in this case. P-values of ≤0.01 were considered significant in these comparisons. The excel function ‘T.TEST’ was used to conduct the tests. Average and peak values and standard deviation of the collected pain ratings have been calculated for the complete set of 1.5 mA and 2.5 mA experiments.

3.4. Experimental Part: Results

3.4.1. Safety and Side-effects

Apart from one experiment which had to be repeated due to flat batteries, all other experiments were conducted without complications and no other experiment had to be aborted. Over the course of the study, subjects continuously reported a mild tingling or itching sensation during stimulation which had a general tendency to attenuate slightly with stimulation time. In few cases there was a mild transient reddish skin irritation at the electrode sites which disappeared within less than one hour. None of the subjects reported any side other side effects like headache, fatigue or mood changes during or after an experiment. Average pain ratings were 1.23 ± 0.45 out of 10 (at 1.5 mA) and 1.71 ± 0.53 out of 10 (at 2.5 mA) while peak pain ratings were 2.48 ± 0.69 (at 1.5 mA) and 3.19 ± 0.75 (at 2.5 mA) out of 10. In general, subjects evaluated the stimulation experiments as not painful. Overall, subjects rated skin sensation as temporarily slightly annoying or slightly uncomfortable at the most. This is well within the known and reported observations of tDCS side effects, as described above.

3.4.2. Impedance and Voltage

As expected, in all measurements prior to and after the experiments as well as during ongoing stimulation, *uniform current-dependent impedance changes were observed*.

The impedance measurements made one minute before and after stimulation revealed a clear tendency of impedance reduction with increasing current magnitude, *even with current strength being in the µA range*. Prior to stimulation, the average impedance (n=18) was 39.4 kΩ ± 8.9 (I = 50 µA), 32.1 kΩ ± 5.1 (I = 100 µA) and 23.7 kΩ ± 4.6 (I = 150-200 µA). Not only average values revealed this tendency, but a decrease of impedance was observed in every single experiment. Measurements made one minute after the experiments (in 1.5 mA and 2.5 mA cases) revealed the same tendency. One minute after five minutes of 1.5 mA tDCS, average impedance (n=10) was 26.2 kΩ ± 12.0 (50 µA), 17.4 kΩ ± 4.2 (100 µA) and 16.4 kΩ ± 1.7 (150 µA). One minute after five minutes of 2.5 mA tDCS, average impedance (n=8) was 15.6 kΩ ± 5.1 (50 µA), 11.1 kΩ ± 2.9 (100 µA) and 10.7 kΩ ± 2.2 (200 µA). In both cases, the general level of impedance was clearly lower after tDCS than prior to tDCS, e.g. 13.2 kΩ lower after 1.5 mA tDCS (at 50µA) and 23.8 kΩ lower after 2.5 mA tDCS (at 50µA). This is an indication towards *a lasting effect of prolonged DC stimulation on skin impedance,* as also investigated by Curdy et al. (37). Moreover, the general level of impedance was lower after 2.5 mA tDCS than after 1.5 mA tDCS, e.g. 10.6 kΩ lower at 50 µA. This is another indication that the

decrease in skin impedance is not only momentary but long lasting and that *the degree of (lasting) impedance reduction depends on the applied current strength, delivered charge density and also current density.* Average impedance values prior to and after stimulation are summarized in Figure 9.

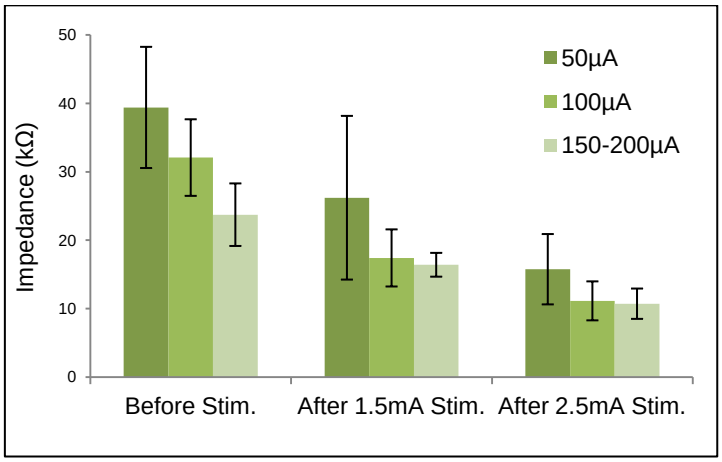

Figure 9: Impedance Prior to and After tDCS

Statistical analysis using Student's t-tests revealed that most of the observed differences were statistically significant ($p \leq 0.01$), even with such small sample sizes. All grouped comparisons which were made are listed in Table 2, with a star indicating statistical significance.

Prior to tDCS	50µA vs. 100µA	*
	50µA vs. 150µA	*
	100µA vs. 150µA	*
Prior to vs. after 1.5mA tDCS	50µA vs. 50µA	*
	100µA vs. 100µA	*
	150µA vs. 150µA	*
Prior to vs. after 2.5mA tDCS	50µA vs. 50µA	*
	100µA vs. 100µA	*
	200µA vs. 200µA	*
After 1.5mA tDCS	50µA vs. 100µA	*
	50µA vs. 150µA	*
	100µA vs. 150µA	p = 0.511
After 2.5mA tDCS	50µA vs. 100µA	p = 0.056
	50µA vs. 150µA	p = 0.032
	100µA vs. 200µA	p = 0.764
After 1.5 vs. after 2.5mA tDCS	50µA vs. 50µA	*
	100µA vs. 100µA	*
	150µA vs. 200µA	*

Table 2: Student's t-tests Comparing Impedance Measurements

Four cases where $p>0.01$ can be explained by *generally smaller impedance differences in the post-tDCS groups (*Figure 9). Due to the overall reduced impedance level in these groups and also keeping the small sample size (n=8 and n=10) in mind, these cases of

insignificance appear reasonable and could be overcome by larger sample sizes and test current intervals (i.e. 50-200-400 µA). After all, this *statistical analysis strongly supports the notion that impedance is influenced by current magnitude and prolonged current flow*.

In the actual stimulation experiments, the previously reported correlation of current and impedance could be strongly confirmed. Impedance behavior over the entire stimulation session is illustrated in Figure 10. With the fade-in phase being started after 10 seconds, current started to linearly increase towards target current over a 30 second interval. Simultaneously, impedance started to drop rapidly over the entire fade-in phase, approaching 6.4 kΩ (I = 1.5 mA) and 5.4 kΩ (I = 2.5 mA) when target current was reached. Now the constant current stimulation phase started, with the impedance drop first appearing not to continue. However, looking at the entire constant current phase of 300 seconds, a further but *much slower impedance drop can be noted. Over the main stimulation phase, average impedance dropped further from 6.4 kΩ to 4.9 kΩ (I = 1.5mA) and 5.4 kΩ to 3.8 kΩ (I = 2.5mA). This suggests that there is not only an instant current-dependent component to the skin impedance changes (observed during the fade-in), but also an accumulative and duration-dependent influence of current on impedance.*

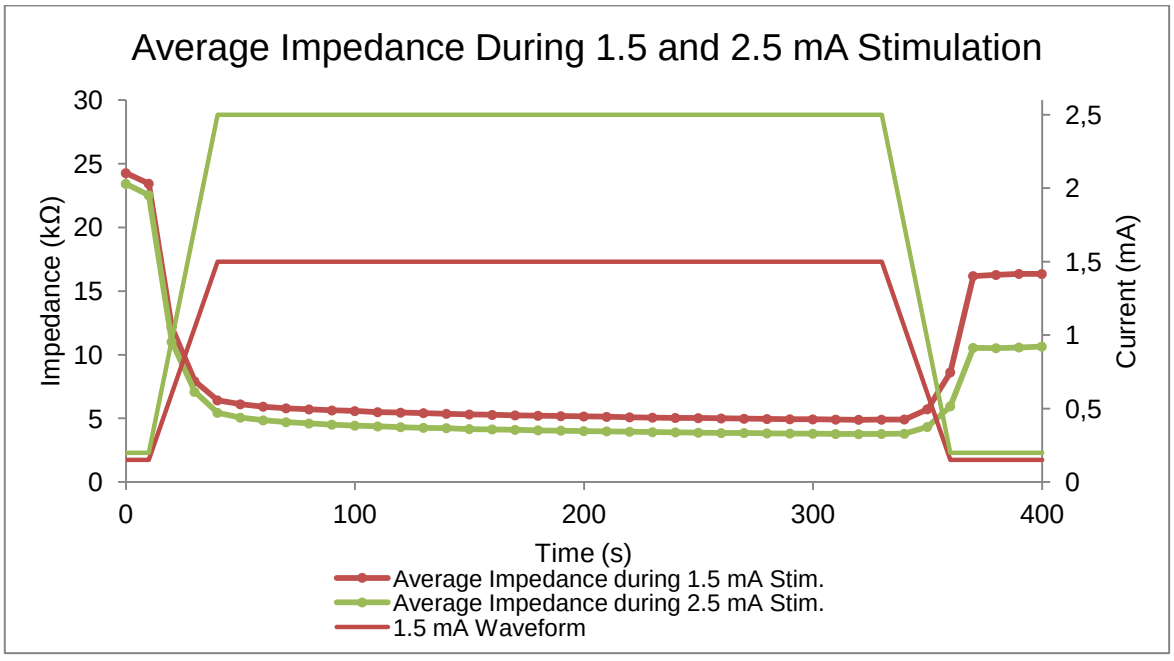

Figure 10: Average Impedance During 1.5 and 2.5 mA tDCS

In the fade-out phase, impedance generally increased with dropping current in a similar but inversed way as during fade-in. As described above, impedance did not reach pre-stimulation levels, and was lower after 2.5 mA than after 1.5 mA tDCS. It appears reasonable to assume that the growing amount of delivered charge over stimulation time plays a major role in this component, which again clarifies the importance of *charge*

density as a parameter of stimulation dosage and safety. The direct influence of current strength on immediate and lasting effects appears also obvious looking at the fact that *the entire impedance profile for 1.5 mA stimulation consists of values lower than the 2.5 mA impedance profile.*

According to Equation 1, *voltage followed the current waveform during current controlled stimulation, while constantly adapting to the described impedance changes*. Voltage increased monotonously during the fade-in phase where current was ramped up, approaching a maximum value when target current was reached. Peak voltage values were 9.63 V ± 2.13 (I = 1.5 mA) and 13.44 V ± 2.25 (I = 2.5 mA), both at the end of the current fade-in phase. These values were significantly smaller than the predetermined maximum output voltages (14.5 and 18.5 V). Looking at all individual cases and not the average, peak voltage values of 13.0 V and 17.7 V were observed. *Hence the maximum output voltage of the stimulator was not reached in any of the experiments.* The course of average voltage is illustrated in Figure 11.

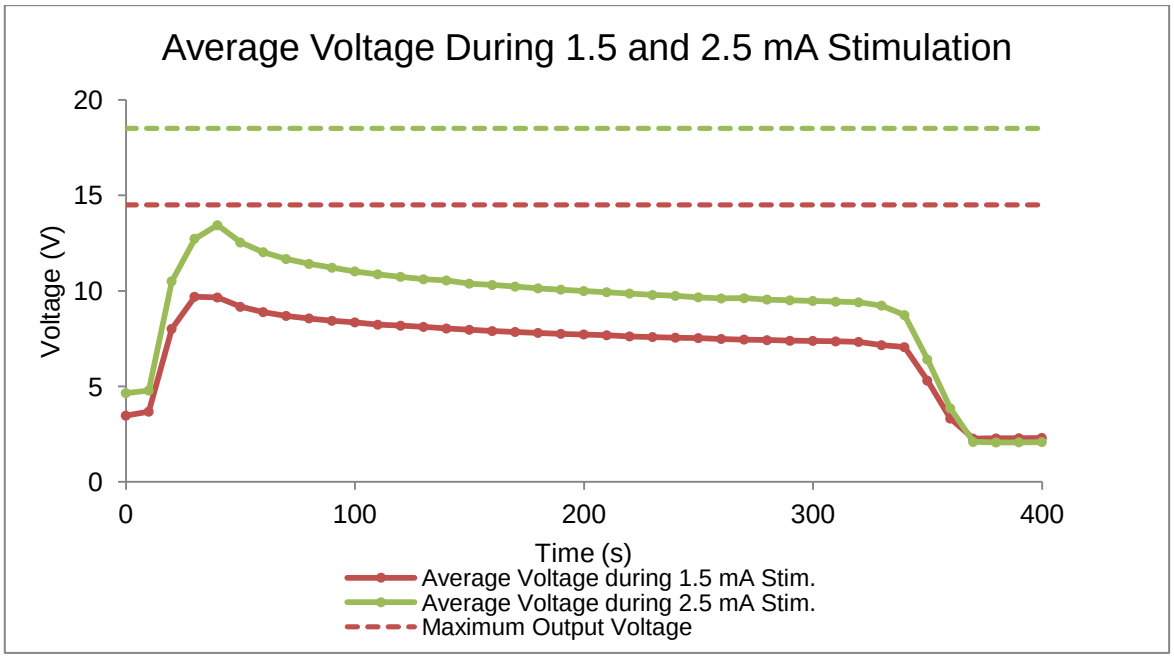

Figure 11: Average Voltage During 1.5 and 2.5 mA tDCS

When current was maintained at target values over the main stimulation phase, voltage across electrodes subsequently dropped due to the described slow impedance drop taking place. Shortly before the fade-out phase was initiated, average voltages were 7.3 V and 9.4 V, proportional to the impedance drops observed in this time interval. After completion of the fade-out phase, offset voltages were lower than prior to stimulation, according to the lasting impedance reduction.

Statistical analysis of voltage recordings indicated that for the top 99th percentile, voltage peaks of 14.1 V (I = 1.5 mA) and 18.3 V (I = 2.5 mA) would be expected. Thus it could be expected that with voltage limits at 14.1 V and 18.3 V, stimulation could be carried out successfully in 99 percent of the cases. In retrospective, the predetermined voltage limits of 14.5 V and 18.5 V in this study were a fortunate choice since they almost match the 99th percentile peak values. The course of the top 99th percentile voltage calculation is shown along with average voltages and voltage limits for 1.5 mA and 2.5 mA cases in Figure 12 and Figure 13.

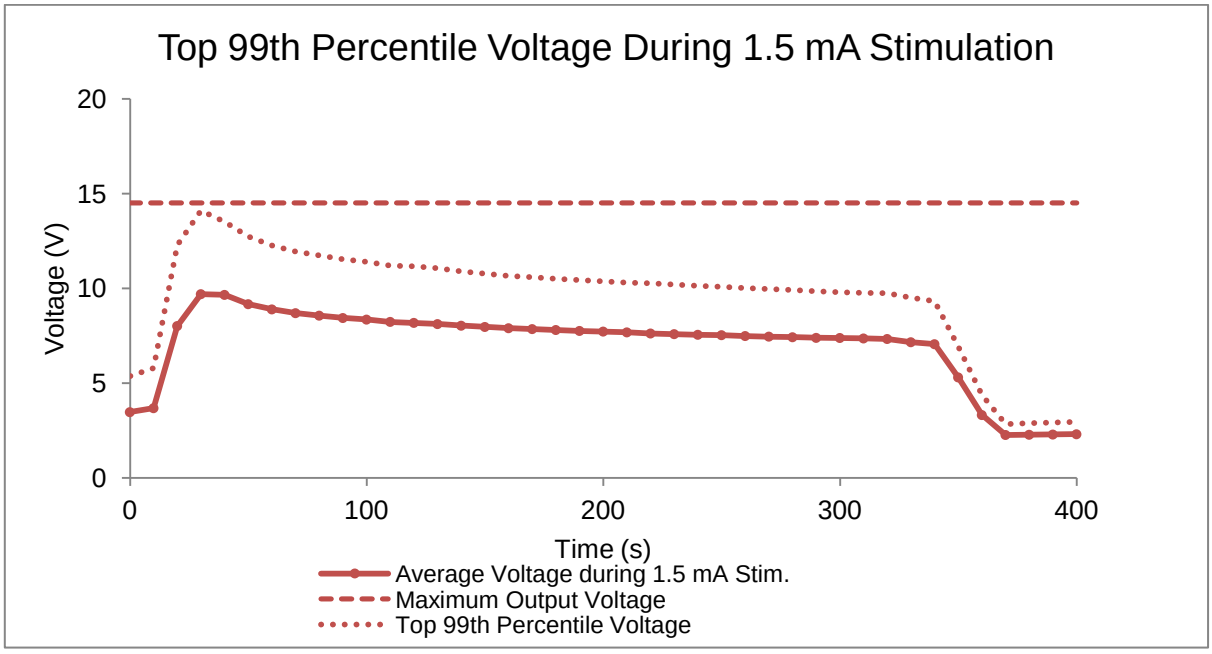

Figure 12: Top 99 % Voltage Interval in 1.5 mA tDCS

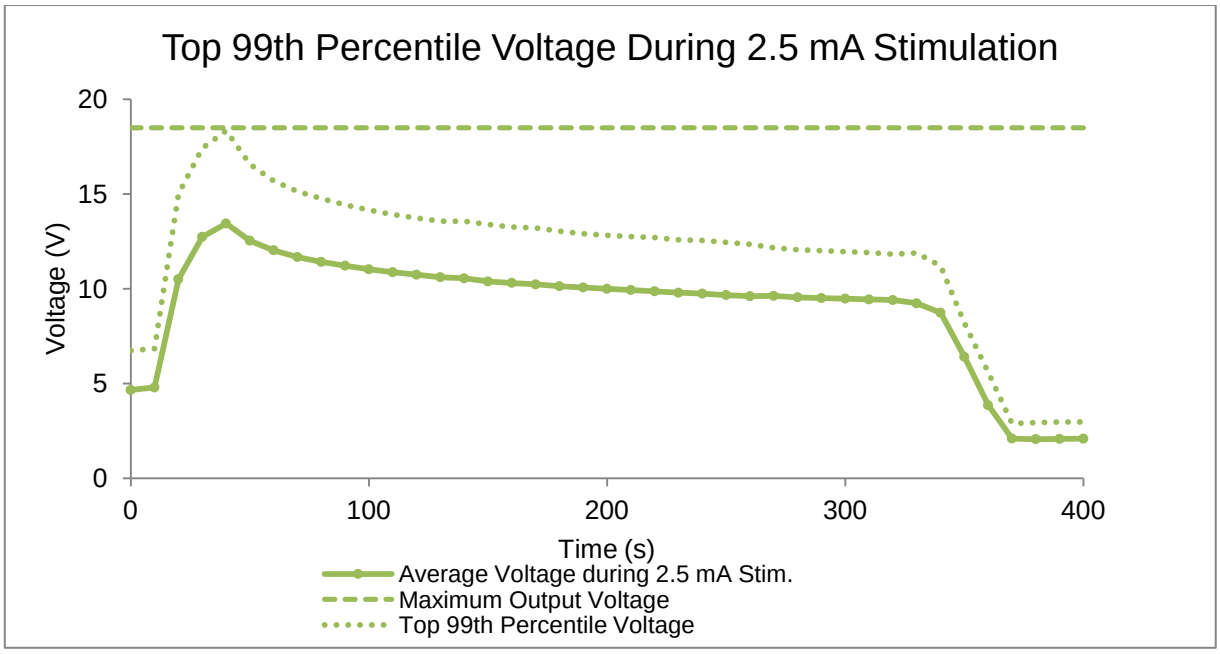

Figure 13: Top 99 % Voltage Interval in 2.5 mA tDCS

4.Conclusions

4.1. General Conclusions and Feasibility of Reduced Voltage tDCS

The data collected and analyzed in this study strongly suggests that reduced (peak) voltage tDCS can be introduced without complications in a range of normally used tDCS setups. *Data analysis supplied conclusive proof of a distinct correlation between skin-electrode-impedance and applied current magnitude, stimulation duration and thus charge density.* It is noteworthy that there is an immediate effect of current flow on impedance across electrodes, followed by a proceeding impedance drop during constant current stimulation. Moreover, the *lasting impedance changes* found after the end of stimulation provide additional proof for the influence of DC stimulation on skin impedance. These findings strongly confirm previously made observations (24, 36-38).

Due to the rapidly dropping impedance during current fade-in, *increasing current intensity does not increase voltage demands to the same extent*. For example, note that given a typical starting impedance of 40 kΩ (measured with I = 50 µA), with no changes in impedance, a compliance voltage of 60 V would be required at 2.5 mA, opposed to an average real compliance voltage of 13.4 V found in this study.

Statistical analysis indicated that voltage limits of 14.1 V for 1.5 mA tDCS and 18.3 V for 2.5 mA tDCS would provide 99% probability of successful stimulation *under the used stimulation conditions*. Given the fact that 2.5 mA current strength is at the very top end of normally used intensities in clinical tDCS studies and applications, it can be concluded that *tDCS voltage limits can generally be reduced to values < 20 V*. Specifically, in a current target specific manner, for 1.5 mA tDCS output voltage of the device can be limited to 14.5 V, whereas 18.5 V is sufficient for successful stimulation at 2.5 mA target current intensity. The proposed values almost match the voltage limits used in this study and leave a small extra security interval compared to the found 99% safety values. Compared to currently available devices having voltage limits of 20 – 43 V, this a valuable contribution towards more safe and comfortable tDCS*, especially in consideration of impedance related skin injuries observed by Palm et al. and Frank et al (25, 26).* According to the results and using normal saline, a voltage limit between 15 and 16 V could be established for the commonly used current magnitude of 2 mA – a value at

least 20% lower than the lowest output voltage (20 V) in all stimulators available on the market.

Compared to the 6.4 - 4.9 kΩ (I = 1.5 mA) and 5.4 - 3.8 kΩ (I = 2.5 mA) average impedances found in the main stimulation phases of the experiments here, Palm et. al observed in *tap-water* 2 mA DCS, that "impedance decreased during ramp up, and *were kept below 20 kΩ for the stimulation period*…". A maximum impedance of 20 kΩ at 2 mA in the main stimulation period corresponds to *40 V being applied to the subject for a significant amount of time over the main stimulation period*. Unfortunately Palm et al. did not specify how many subjects had impedances in the 20 kΩ range and if these were the subjects with skin lesions. In the cases reported by Palm et al., skin injuries occurred after four or five tDCS session. With all given information it can be suspected that four 20 minute long tDCS sessions over four days at 2 mA and close to 20 kΩ impedance, combined with non-uniform current distribution, led to the observed skin burns.

The limitation of output voltage to 20 V and lower suggested in this study may help to prevent this. Average voltage found by Dundas et. al, using normal saline, was similar and even lower compared to values found in this study, with an average of ~4.5 V at 1 mA tDCS (corresponding to 4.5 kΩ). Here, larger sponges were used, what possibly explains even lower impedance through smaller current density.

Interestingly, the notion that the use of tap-water leads to smaller skin sensation was one motivation to use tap-water in the cases reported by Palm et al., and supposedly led to skin injury in form of lesions. Another motivation to use tap-water was the necessity for EEG recordings in that study. This should be noted as one limitation of reduced-voltage tDCS: In order to achieve low impedance and voltage, normal saline has to be used, which rules out the possibility for EEG recordings since saline interferes with the EEG.

However, specifically in intensive repeated daily application of tDCS, a (peak) voltage reduction seems to be viable to reduce the risk of skin injury since the reported incidents happened after multiple tDCS session. Moreover, reduced voltage tDCS may be especially useful for application in vulnerable populations; i.e. pediatric or geriatric populations where patients more likely have sensitive and vulnerable skin.

Apart from a reduction of output voltage, a novel approach to current/voltage control and limits which is taking advantage of the found impedance behavior during tDCS is discussed below. This is also aiming at the previously described cases of stimulation abortion where target current was not reached due to high impedance.

4.2. Limited Total Energy tDCS: An Improved Stimulation Protocol for tDCS

As mentioned above, another goal of this study was motivated by reports of tDCS devices aborting stimulation when high impedance was encountered. These cases in a tDCS study for depression patients are unpublished and were communicated personally. In the described cases, high impedance across electrodes (usual carbon rubber pads with saline soaked sponges) was encountered in several cases. As a result of this, the used tDCS devices which were limited to 26 V could not reach the 2.5 mA target current and subsequently aborted stimulation automatically without warning the operator and leaving a chance to refine the setup. In this case, the tDCS device apparently interpreted the voltage limit as a safety threshold and not as a simple boundary for output voltage. The author calls this a 'hard voltage limit'. The used stimulator was apparently designed to automatically abort stimulation when hitting this threshold. For different reasons, this is unfortunate – as mentioned before it is a disturbance of the clinical work flow and an inconvenience for the patient who has to undergo the tDCS procedure again after abortion.

Looking at the results of this study, particularly the impedance characteristics during tDCS, another approach which is described here seems worthwhile. Considering the monotonous drop of impedance both during the phases where current is ramped up and then being held constant, the stimulator can be allowed to *maintain voltage at maximum level* (*which is already reduced compared to other devices*). If high impedance is encountered, *target current will not be reached during the normal fade-in phase and voltage will then be maintained at maximum level as long as target current is not reached*. Data collected in this study suggests, that in all cases *impedance will continue to drop monotonously*, even when current intensity is reduced and not at target. With voltage being maintained at maximum level (e.g. 14.5 V for 1.5 mA tDCS or 18.5 V for 2.5 mA), *current will then continue to increase, only in a slower and nonlinear way.* A linear current ramp is the standard fade-in procedure, but there is no indication that a slower nonlinear current ramp has any negative influence on tDCS except from an increased duration of the fade-in phase. Only a current increase *faster* than a linear ramp would be unfavorable (due to possibly increased skin sensation), but can generally be ruled out in case of current controlled fade-in. *Under the assumption that a prolonged and variable fade-in phase at the beginning can be tolerated to some extent (e.g. max. 3 minutes length),* the new stimulation protocols key factors are:

- Current controlled stimulation
- Reduced voltage limit, *variable according to the preset target current*
- The voltage limit is ‘soft’ – voltage may be maintained at this limit for a predetermined amount of time
- In case of high impedance, the device maintains voltage at maximum and “waits for impedance to drop” in order to gain target current
- This is indicated clearly to the operator by an acoustic or rather visual signal
- If target current cannot be reached within a predetermined amount of time (e.g. 3 minutes), this is indicated by another rather acoustic signal and followed by stimulation abortion
- Clearly legible displays indicate real current and voltage values at all times

If a case of high impedance is encountered, the operator now has a chance to judge the situation (e.g. if current is already close to target and will reach it within one or two minutes or if impedance is very high and a correction of the electrode setup is necessary). This increases the chance that stimulation can be carried out successfully. For example the operator can add saline solution to the electrodes or enhance electrode-skin contact by applying soft pressure and massage.

As another feature to help prevent troublesome cases, *intelligent* (target current dependent) pre-stimulation impedance checks can be implemented into the stimulator device. These are ideally based on target current and experimentally determined threshold values. For example, when target current is adjusted to 2.5 mA, the stimulator could use a test current of 50 µA and indicate high impedance when ≥ 40 kΩ are measured. Lower target current will be accompanied by a lower voltage limit and a matched impedance threshold. This way, the operator has a chance to

- Maximize the chance for successful stimulation *before* starting tDCS
- Further improve the electrode setup *during* the prolonged fade-in phase

With this technology, stimulation will only be aborted in extremely unlikely cases of *extraordinarily* high impedance which cannot be decreased with the usual methods. According to the protective and energy limiting nature of this new tDCS protocol, it has been named *Limited Total Energy tDCS* (LTE-tDCS).

Figure 14 exemplifies LTE-tDCS alongside normal tDCS in a schematic way for five different possible impedance profiles, the red case being critical. Here, it can be seen that during LTE-tDCS there is no case of abortion when high impedance is encountered and that voltage always stays in the green low-voltage interval. Still, it is noteworthy that under optimal low-impedance conditions, normal tDCS and LTE-tDCS behave alike (indicated by the light green, orange and blue cases), and only *in critical cases (dark green and red) LTE-tDCS provides extra protection and better chance for successful stimulation compared to normal tDCS.*

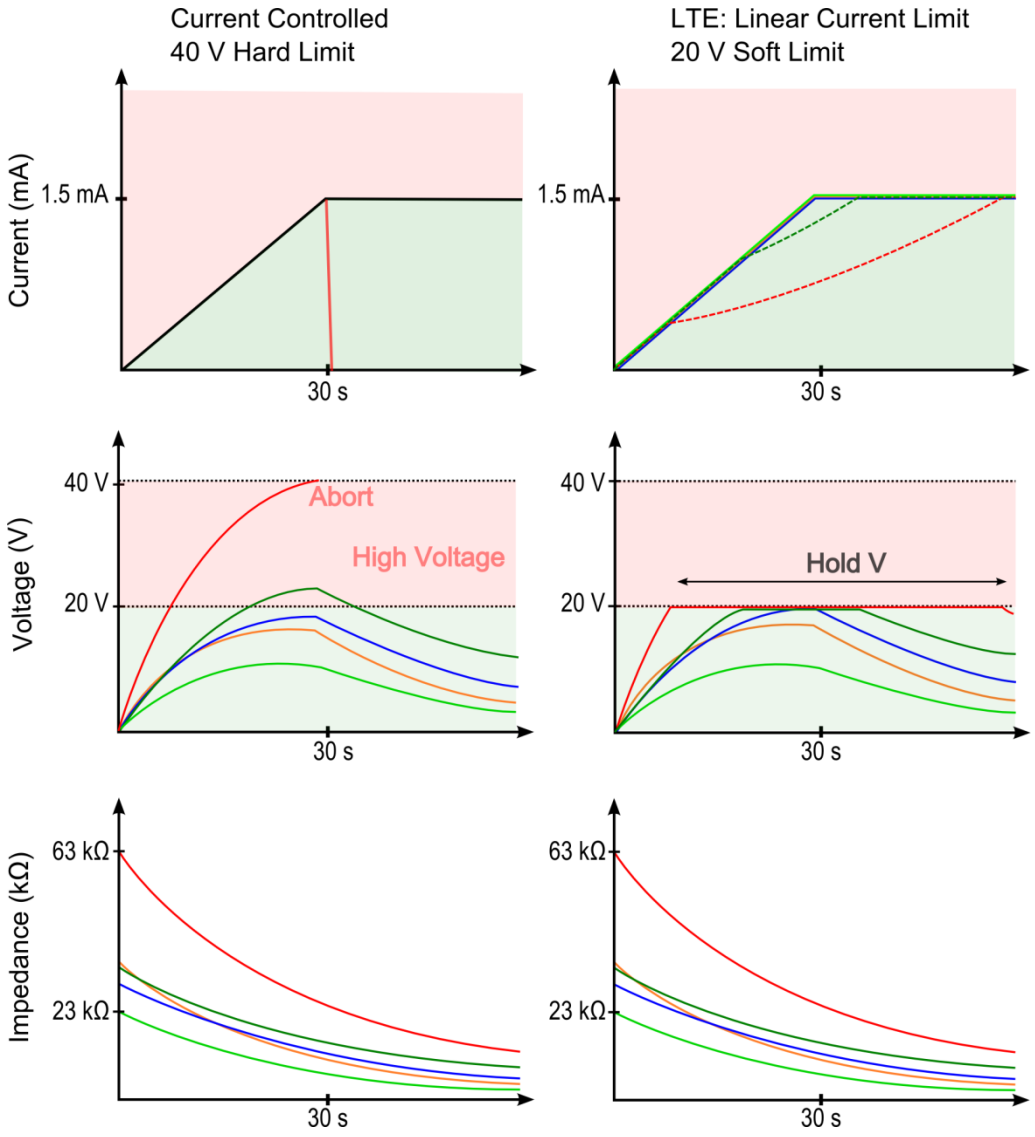

Figure 14: Regular vs. LTE-tDCS

The concept of LTE-tDCS limits the *peak* voltage and together with improved electrode preparation improves the chances of succesful stimulation protocols. Even in LTE-tDCS, the *overall* impedance level is still mainly determined by the way the operator prepares and attaches tDCS electrodes.

4.3. The Crucial Role of Electrode Preparation

As it has been described in detail, the way electrodes are set up and prepared is a key factor for functional and practical aspects of tDCS. Impedance as a crucial parameter for tDCS in general and particularly for LTE-tDCS, is mostly influenced by a proper preparation and setup of the electrodes. In order to guarantee successful application of LTE-tDCS and to minimize the overall impedance level of the setup, it is indispensable that the operator is well educated about the relation of voltage and impedance, impedance related skin burns and possible actions to lower impedance across electrodes. The operator needs to be trained to setup and prepare electrodes in a proper way and needs to know how he should react in case of complications. This can happen in person and/or through educational videos (57).

Together with improved education and electrode preparation skills of the operator, the concept of LTE-tDCS with implemented intelligent impedance monitoring and extra-low peak voltage enables succesful delivery of safer electrical stimulation at persistent intensity and efficacy.

4.4. Limitations of this Study

Even though this study resulted in an improved and robust new design for low-voltage tDCS, some limitations have to be noted. It is reasonable to expect that the proposed LTE-tDCS design, including determined voltage limits, will successfully function in a wide range of mainstream tDCS applications. Changing key stimulation conditions like using a different electrode type, using more than two electrodes, substituting saline with tap water (for example when EEG is recorded simultaneously), using very small amounts or no saline, or using electrode montages with significantly larger electrode distance can possibly lead to unsuccessful stimulation due to insufficient output voltage. However, all electrode montages placing two rubber carbon electrodes / saline sponges on the head with a similar distance like M1-SO are suitable for use with LTE-tDCS, using determined target-current-dependent voltage limits. These include the most commonly used montages M1-SO, DLPFC-SO, OZ-CZ, M1-M1 and DLPFC-DLPFC.

The sample sizes used in this study were large enough to observe significant effects and the same qualitative observations were made in each experiment. However, this cannot distract from the fact that sample sizes were small. In order to confirm the results, more data from a higher number of subjects should be collected in the future.

For reduced voltage LTE-tDCS with higher current strength, more electrodes (for example HD-LTE-tDCS with five electrodes) and/or different electrode types (Ag/AgCl or

even self-adhesive electrodes) voltage limits will need to be determined in separate experiments.

The developments made in this thesis are considered a contribution towards patient safety, particularly to avoid skin injuries in tDCS. It remains uncertain, if they also improve patient comfort in the sense of reduced skin sensation. As described above, skin sensation seems to be influenced by the use of saline and by saline concentration (23). Voltage magnitude may also influence skin sensation, but likely not to the same extent as saline concentration. Further studies would be necessary to investigate if LTE-tDCS, which requires a fair amount of normal saline, causes stronger skin sensation than regular tDCS with higher voltage and tap water or low-concentration saline being used. *However, subjects did not report abnormal skin sensation in this study, and skin safety (in terms of a voltage reduction) has a higher priority than skin sensation (in terms of lower concentrated saline).* In future studies, it appears also worthwhile to investigate the use of calcium chloride ($CaCl_2$) solution instead of saline, which has been observed to cause smaller skin sensation by Kalia and Guy (38).

5.Afterword

The work done in this study and thesis has been summarized in another article, which will be submitted for publication to the journal *Clinical Neurophysiology*. On January 13th 2012, The City College of New York filed a United States patent called 'Voltage Limited Neurostimulation', partly based on this work, with the inventors Marom Bikson, Christoph Hahn, Shiraz Macuff, Preet Minhas, Asif Rahman and Justin Rice.

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6.2. Lists of Figures and Tables

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