Historical notes on transcranial electrical stimulation: Doses and Approaches

Berkan Guleyupoglu\textsuperscript{a}, Pedro Schestatsky\textsuperscript{b}, Felipe Fregni\textsuperscript{c,d}, and Marom Bikson\textsuperscript{a}

\textsuperscript{a} Neural Engineering Laboratory, Department of Biomedical Engineering, The City College of New York of CUNY, New York, NY 10031, USA
\textsuperscript{b} Department of Internal Medicine, Universidade Federal do Rio Grande do Sul, CAPES, Brazil
\textsuperscript{c} Laboratory of Neuromodulation, Spaulding Rehabilitation Hospital, Harvard Medical School, Boston, MA 02114, USA
\textsuperscript{d} Berenson-Allen Center for Noninvasive Brain Stimulation, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02215, USA

Review

Total Document Length: 28 Pages

<table>
<thead>
<tr>
<th>Page Numbers</th>
<th>Section Title</th>
<th>Section Length</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Title and Abstract</td>
<td>1 Page</td>
</tr>
<tr>
<td>2-17</td>
<td>Main Body</td>
<td>17 Pages</td>
</tr>
<tr>
<td>18-22</td>
<td>References</td>
<td>5 Pages</td>
</tr>
<tr>
<td>23</td>
<td>Figure Legend</td>
<td>1 Page</td>
</tr>
<tr>
<td>24-25</td>
<td>Table Legends</td>
<td>2 Pages</td>
</tr>
</tbody>
</table>

Berkan Guleyupoglu
Department of Biomedical Engineering
The City College of New York
160 Convent Ave.
463 Steinman Hall
New York, NY 10031

Lab Phone: +1- 212-650-8653
Fax: +1-212-650-6727
Email: bguleyup@gmail.com
Historical notes on transcranial electrical stimulation: Doses and Approaches

Berkan Guleyupoglu, Pedro Schestatsky, Felipe Fregni, and Marom Bikson.

Abstract

Transcranial Electrical Stimulation (tES) encompasses all methods of non-invasive current application to the brain used in research and clinical applications. We present the first comprehensive and technical review, explaining the evolution of tES in both terminology and dosage over the past 100 years of research to present day. Current transcranial Pulsed Current Stimulation (tPCS) approaches such as Cranial Electrotherapy Stimulation (CES) descended from Electrosleep (ES) through Cranial Electro-stimulation Therapy (CET), Transcerebral Electrotherapy (TCET), and NeuroElectric Therapy (NET) while others like Transcutaneous Cranial Electrical Stimulation (TCES) descended from Electroanesthesia (EA) through Limoge, and Interferential Stimulation. Prior to a contemporary resurgence in interest, forms of transcranial Direct Current Stimulation were explored intermittently, notable as polarizing current. The development of these approaches alongside electroconvulsive therapy (ECT) and pharmacological developments are considered. Both the roots and unique features of contemporary approaches such as transcranial Alternating Current Stimulation (tACS) and transcranial Random Noise Stimulation (tRNS) are discussed. Trends and incremental developments in electrode montage and waveform spanning decades are presented leading to the present day. Commercial devices, seminal conferences, and regulatory decisions are noted, though emphasis is placed on relevance and insight into current practices.
1. Scope and Approach

Transcranial Electrical Stimulation (TES) encompasses all forms of research and clinical application of electrical currents to the brain non-invasively using (at least one) electrodes on the head. The dose of TES is defined by the electrode montage and the stimulation waveform applied to the electrode (Peterchev et. al., 2012). There has been a resurgence of interest since 2000, but “modern” TES developed incrementally over a century. This review attempts to provide the first comprehensive organization of approaches and dose used in modern TES since 1900.

This process involves defining the litany of terminology that has developed and evolved around TES. We make no attempt to re-define or qualify any approaches used, but explain the terminology as used contemporarily by researchers. Particular attention is paid to historically linked categories of TES, “streams”, of which we identify four that span decades plus “contemporary” approaches (Figure 1).

1) Cranial Electrical Stimulation (CES) descended from Electrosleep (ES) through Cranial Electrostimulation Therapy (CET), Transcerebral Electrotherapy (TCET), and NeuroElectric Therapy (NET).
2) Electroanesthesia went through several periods of waning interest and resurgence when new waveform variations were proposed including Transcutaneous Cranial Electrical Stimulation (TCES), Limoge, and Interferential Stimulation.
3) Polarizing or Direct Current Stimulation includes recent transcranial Direct Current Stimulation, Transcranial Micropolarization, High-Definition transcranial Direct Current Stimulation (HD-tDCS) and Galvanic Vestibular Stimulation (GVS).
4) Electroconvulsive Therapy (ECT), initially called Electroshock Therapy, evolved in technique and dose, such as Focal Electrically Administered Seizure Therapy (FEAST).
5) Finally, we categorize “contemporary” approaches that have been explored intensely over the last decade, such as transcranial Alternating Current Stimulation (tACS), transcranial Sinusoidal Direct Current Stimulation (tSDCS), and transcranial Random Noise Stimulation (tRNS). Though analogues to these
contemporary approaches can be identified in earlier literature, contemporary approaches contain dose features that motivate us to consider them novel. Contemporary approaches to some extent reflect a “re-boot” of tES approach, typically employing basic, well documented, and well-defined waveforms (e.g. one sinusoid; Paulus, 2011) in contrast to the increasingly complex waveforms developed (though not always justified) over decades in some streams.

As our technical focus is on dose clarification and classification, we minimize comments on the clinical efficacy or safety of any approaches except in special cases where findings resulted in historically notable and sudden changes in dose or terminology. We note specific conferences and regulatory agencies that helped identify and shape the field of Transcranial Electrical Stimulation including establishing terminology. Commercial (brand) names of devices are noted *ad hoc* for context and linked to dose terms where appropriate. We do not comment directly on mechanisms but emphasize that dose determines electric field in the brain (Peterchev et. al., 2012) which, in turn, gives rise to neurophysiological responses (Bikson et. al., 2004); thus understanding the dose is a prerequisite to understanding mechanisms.

We do not address magnetic stimulation approaches or electrical stimulation approaches not targeting the brain, or non-electrical therapies, except in specific cases to indicate the terminology used in these other approaches for the purpose of overall clarity of nomenclature. We did not attempt to perform an exhaustive cataloging of tES publications.

Though we do not comment on efficacy, the nominal indications for tES use (intended clinical outcomes) are noted when contextually relevant, especially for many historical streams (defined above). There are instances in which researchers used terminology to describe a dose in a manner potentially inconsistent with typical historical norms of dose associated with that terminology - when these papers provide sufficient dose details these deviations are noted. Our summary aims to reflect the most typical doses used across the majority of studies (Table 1). In addition, to promote a more
comprehensive and systematic dose classification, we propose new categories for those waveforms using pulsed stimulation in table 2 (transcranial Pulsed Current Stimulation, tPCS).

It is important to emphasize that the specifics of tES dose (electrode montage and waveform) determine brain modulation – evidently the given therapy name is incidental and often reflects a historical bias and varying intended use. In this sense, a strict approach would involve ignoring all historical nomenclature and consideration of specific dose. However, this ideal approach is problematic due to the following reasons: a) In most cases, the complete dose details are not provided (e.g. electrode size, waveform details); b) investigators often adjusted dose resulted in hundreds of potential categories.

Ultimately, this review should serve as a road map for further investigation of classical techniques and appreciation of the origin of recent techniques. Even experienced researchers may remain unclear about basic features in classical literature, for instance, did ElectroSleep use DC? At the same time, the broad view taken in this review should be a useful introduction to new investigators and clinicians. More generally, we are interested in the narrative of tES development with respect to current tES clinical studies. Research into tES mechanisms in clinical outcomes has been active for over a century. Some specific dose approaches (with indications) generated increased interest only later to be largely abandoned – the context for such waxing and waning of enthusiasm for specific historical approaches, may be relevant for current clinical efforts. Similarly, the history of tES development reflects parallel developments in pharmacology including narcotics – which again may provide perspective on current clinical trials (Brunoni et. al., 2012). Our intention is that this historical dose analysis of tES, with requisite clarification and definition of dose terminology, will provide context on current approaches and facilitate rational investigation and adoption.

2. Historical Development
2.1 Developments from Electrosleep to Cranial Electrotherapy Stimulation

Electrosleep (ES), in short, is the name for tPCS methods by which the brain was stimulated in order to induce a sleep-like state in the subject. The first studies on electrosleep initiated in 1902 (Gilula and Kirsch, 2005), however, the first clinical report of electrosleep was published 12 years later (Brown, 1975). Most of the research regarding electrosleep was conducted in Russia up until 1953, when clinical use of electrosleep began in Europe (Smith, 2006). New approaches were developed mostly in Europe, such as changing electrode position from covering the eyes to locations around the eyes, presumably to reduce optic nerve irritation (Brown, 1975). Electrosleep dose waveform was typically pulsed at 30-100 Hz, but at least one (unsuccessful) case of use of DC current was documented (Brown, 1975). After 1963, an increased use of electrosleep in the United States was noted. Three years later, the first symposium on Electrosleep and Electroanesthesia was held in Graz, Austria (Smith, 2006; Knutson, 1967). At this symposium it was reasoned that electrosleep does not actually induce sleep, rather it is an indirect side effect of the relaxing effects of stimulation. Therefore, the name of electrosleep was changed to Cranial Electrostimulation Therapy (CET) (Knutson, 1967). This was the first of several changes of the name of Electrosleep over the next few decades, often with notable changes in dose. Some devices that were used during this time were: Jungbluth CET-1, Tritronics 100, Somatron 500, Lafayette 72000, Lafayette 72200, and General Medical Industry 1-1007-1 (Brown, 1975).

In 1969, Transcerebral Electrotherapy (TCET) was proposed as another alternative name, which was adopted by some authors (Brown, 1975). In 1977, electrosleep and its derivatives went under review by the FDA and in 1978 were classified as a Class III device for the treatment of Anxiety, Insomnia, and Depression (FDA Executive Summary, 2012). However, such devices were re-named as
Cranial Electrotherapy Stimulation (CES) (Kirsch, 2010). The FDA status of CES remains debated to the present day (FDA Executive Summary, 2012).

In 1972 a new method and device of electrosleep called NeuroElectric Therapy (NET) (Patterson, 1976; Patterson, 1979) was developed in England. Though NET preceded many modern CES devices (see below) it may have influenced the doses they used decades later. Another notable device, produced after the name change to CET, was the Neurotone 101, which was based on a Russian ES device brought to the United States. Although the Neurotone 101 is no longer in production, it was the first device to be approved by the FDA as a CES device (Kirsch, 2010) and all subsequent CES devices approved by the FDA were through a 510k process claiming equivalency, either direct or descendent, to the Neurotone 101. This equivalency is not reflected in identical dose of current CES devices, which in fact are often claimed to be a novel dose.

Modern Cranial Electrotherapy Stimulation (CES) is thus a historical descendant of Electrosleep even as dose and indications have continuously evolved.

2.2 Developments From Electroanesthesia to Limoge Current and Other Related Methods

Electroanesthesia (EA), in short, was intended to induce anesthesia in the subject so that chemicals did not have to be used pre-surgery. Electroanesthesia studies started in 1903 but were first known as Electronarcosis (EN) (Brown, 1975; Limoge et. al., 1999). Russian scientists used the term "electroanesthsia" to describe local anesthesia while "electronarcosis" described general anesthesia (Brown, 1975). However, electroanesthesia stopped being referred to as local, applied to the periphery, and began to be known as general anesthesia, now applied to the brain. Therefore, in this review, EA will refer to general anesthesia. One of the earliest published claims of success in regards to EA during surgery was made in 1914 by Leduc (Brown, 1975; Smith, 1971). Safety and tolerability concerns, and the development of early chemical anesthetics, may have contributed to quelling interest in EA. In the
1940s research on EA focused on chemical primers being used in conjunction with EA (Brown, 1975). Soon after, research appeared to largely halt again presumably due to severe side effects. For example, severe side effects such as cardiac arrest, respiratory arrest and apoplexy were observed (Knutson, 1956; Smith et. al., 1967). A third wave of research in EA initiated after a study was published in 1960, proposing a new EA approach to reduce side effects: “...a combination of pulsed and direct currents...the very slow increase of current levels... and...the use of a generator that minimized changes in electrode impedance resulting from polarization (Brown, 1975)” (Smith et. al., 1966).

Research into EA dosage continued and the term Transcutaneous Cranial Electrical Stimulation (TCES) was adopted around 1960-1963, with the intended use to “potentiate some drug effects, especially opiates and neuroleptics, during anesthetic clinical procedures...[with the goal of] drastic reduction in pharmacologic anesthetic agent and reducing post-operative complications” (Limoge et. al., 1999). Even though the term TCES was not adopted until the early 1960s, similar protocols were used as early as 1902 by Leduc (Limoge et. al., 1999). In 1951, Denier proposed that high frequency trains of 90 kHz could be used to avoid muscular contraction (Limoge et. al., 1999). Three years later, Knutson (1954) claimed that alternating currents at 700 Hz should be applied, but this was abandoned in 1958 due to cardiovascular complications (Limoge et. al., 1999). In 1957, investigators in the Soviet Union attempted to add a DC component to Leduc’s currents but, as claimed by an American scientist Robert Smith, it resulted in a collection of undesirable side effects (Smith et. al., 1966). In 1963, Aimé Limoge modified the TCES dose and called it Limoge Current (Limoge et. al., 1999). In 1964, a study claimed pulsating currents are more effective than direct currents for the induction of EA (Brown, 1975). Another study suggested that the use of pure DC for EA required high intensity of approximately 40 mA (Brown, 1975).

In 1965, Interferential Stimulation (IS) was proposed by Russian scientists (Brown, 1975). IS consisted of having two pairs of electrodes energized with sine waves of slightly shifted frequencies. Through pulsation the higher frequencies would create a lower frequency, where the two
frequencies intersect. This was done because low frequencies were more desirable in inducing EA whereas higher frequencies were more desirable when it came to patient comfort (i.e., reduced pain, sensation, etc.) (Brown, 1975; Smith, 1971). In this way lower frequencies were indirectly combined with high frequencies— an approach also hinted at in some CES technologies. Even though power is modulation, under the assumption that the time-constant in neuronal membranes effectively filters out high frequency signals (> 100 Hz; Bikson, et. al., 2004) then regardless of how they are combined and modulated, these signals would be neurophysiologically inactive.

In the development of EA, **Fading** has two different meanings, decrease in anesthetic state (Smith et. al., 1968) or increase in tolerability. In the first case, fading indicated a decrease in the subjects’ anesthetic state while the dosage was kept steady (Smith et. al., 1968). Maintenance of anesthetic state was accomplished by either reduction of frequency or increase of current (Smith et. al., 1968). Fading, more recently, has been used to increase tolerability by incremental increase to the maximum dosage under the premise that sensation at the skin adapts to current flow. Indeed, fading is a common method used in many contemporary tES approaches such as tDCS. TCES has been studied to reduce post-operative analgesic requirements (Nekhendzy et. al., 2010), as are other contemporary tES approaches (Borckardt et. al., 2011).

Contemporary tES is also concerned with the treatment of a broad range of neuropsychiatric disorders, including pain (Zaghi et. al., 2011; Brunoni et. al., 2012; Brunoni et. al., 2013). Historically, EA/TCES used current intensities typically well above those used in contemporary tES. None-the-less, these relatively high intensity EA/TCES approaches provide insight into (upper) safety limits and approaches to enhance tolerability, and broad indications of responsive conditions when applied alone or with pharmacotherapy.

**2.3 DC Stimulation**
Direct current stimulation has been used intermittently as a component in both ES and EA. In 1957, a DC bias was added to ES which is traditionally applied using only AC. The advent of TCES, around 1960-1963, in the third resurgence of EA research, also incorporated a DC bias. In 1969, pure direct current stimulation was investigated for inducing anesthesia (Brown, 1975). However, it was not until 1964 that preliminary studies heralding modern transcranial Direct Current Stimulation (tDCS) were published.

In 1964, Redfearn and Lippold investigated polarizing current for treatment of neuropsychiatric diseases (Redfearn and Lippold, 1964), their use of prolonged (minutes) or stimulation was motivated by animal studies showing that prolonged direct current stimulation could produce lasting changes in excitability. Short duration tDCS was investigated by Priori and colleagues in 1998 (Priori et. al., 1998). Nitsche and Paulus established that prolonged tDCS could produce lasting and polarity specific changes in cortical excitability (Nitsche and Paulus, 2000) followed by pilot clinical studies (Bolognini et. al., 2009). Transcranial Micropolarization is a technique investigated in Russia which is modified version of tDCS using small electrodes instead of pads (Shelyakin and Preobrazhenskaya, 2009). In 2007, High Definition transcranial Direct Current Stimulation (HD-tDCS), was proposed a focalized form of tDCS (Datta et. al., 2009). HD-tDCS uses specially optimized electrodes (Minhas et. al., 2010), arranged in arrays that can be optimized per indication (Dmochowski et. al., 2011), including the 4x1 configuration (Edwards et. al., 2013).

Galvanic Vestibular Stimulation (GVS) is being investigated for effects on ocular and postural movement (Watson and Colebatch, 1997). Alongside GVS, Caloric Vestibular Stimulation (CVS) is under investigation due to similar areas being targeted by stimulation. However, CVS does not utilize electricity, rather irrigation of the ear canal using cold or warm water (Miller and Ngo, 2007).

2.4 ECT
Initially developed circa 1933, **Electroconvulsive Therapy (ECT)** (Gilula and Kirsch, 2005; Abrams, 2002), used repetitive high-intensity pulses to trigger seizures. A common moniker used for ECT is **Electroshock Therapy (EST)**. ECT was cleared by the FDA for Depression in 1976 as a “pre-amendment device” (“grandfathered” similar to the process CES). In 2011 the FDA summarized: “The ECT procedure was first conducted in 1938 (Rudorfer et. al., 1997). Two Italian physicians, Ugo Cerletti and Lucio Bini, guided by a theory holding an antagonistic relationship between seizures and psychosis, became the first to use electricity to induce a therapeutic seizure in humans (Faedda et. al., 2010). They reported on the first treatment of a patient using this method in 1939 (Bini, 1995). Joining a number of other somatic-based therapies of the era (prior to the advent of modern pharmacotherapy), ECT became a popular intervention for psychiatric conditions. Since that time, the use of ECT has waxed and waned.

In the 1950’s and 60’s, with the development of drug therapies for psychiatric conditions, and due to concern for serious device related adverse events, the use of ECT in the U.S. declined (Lisanby, 2007). However, in recent years, interest in, and use of, ECT has experienced a resurgence; ECT use in the U.S. has been estimates at 100,000 individuals receiving this treatment annually (Hermann et. al., 1995). Reflecting the greater proportion of women who suffer from major depression, two-thirds of patients who receive ECT are women (Olfson et. al., 1998). In clinical practice, ECT is generally considered after failure of one or more antidepressant medication trials, or when there is need for a rapid and definitive response (APA 2001; p. 23-24). ECT has been used to treat a variety of psychiatric disorders. These disorders include: Depression (unipolar and bipolar), Schizophrenia, Bipolar manic (and mixed) states, Catatonia, Schizoaffective disorder. The evidence supporting the effectiveness of ECT for each of these indications is variable.”

### 2.5 Contemporary approaches
Two contemporary forms of tES are **transcranial Alternating Current Stimulation (tACS)** and **transcranial Random Noise Stimulation (tRNS)** (Paulus, 2011). Both tACS and tRNS use relatively low-intensity current and are being investigated for therapeutic effects (Paulus, 2011). A modified protocol for tACS is **transcranial Sinusoidal Direct Current Stimulation (tSDCS)** (Antal et al., 2008) where the stimulation is monophasic due to a DC bias added to the sinusoid.

Another form of tES that was used by Marshall and colleagues (Marshall et al. 2006) consisted of monophasic trapezoidal pulses with a DC bias, frequency of .75 Hz. The pulses used by Lisa Marshall were investigated for their effects on learning. The subject would learn the task before sleeping, and be tested on the task the next morning. The stimulation would occur 4 minutes after stage 2 sleep occurred for the first time, without reversion to stage 1, and stimulation continued at 5 minute intervals with a 1 minute break throughout the night (Marshall et al., 2006).

### 2.6 “TES”

The first mention of “TES” was 1980 in a study by Morton and Merton (Merton and Morton, 1980). “TES” uses single (isolated) high-intensity pulses to typically activate motor cortex and stimulate motor response. This early use of “TES” resulted in many contemporary investigators associating “TES” with only supra-threshold low frequency pulses. In this review, we use tES in the broader sense and and “TES” (quotes and capitals) to specify the use of supra-threshold low frequency pulses. “TES” technique can be painful and was not investigated for therapeutic applications, but remains used for diagnostic purposes under anesthesia (Zentner et al., 1989; Macdonald, 2002; Kalkman et al., 1992). For the purposes of experimental with low-frequency supra-threshold stimulation in awake subjects, contemporary investigators often use Transcranial Magnetic Stimulation (TMS) instead, as it is more tolerated for these purposes. “TES” continues to be used for intra-operative evaluation in anesthetized subjects and “TES” was first “cleared” by the FDA in 2002 monitoring.
2.7 Non-Cranial Therapies

Non-cranial electrical therapies are mentioned here only in context of historical relevance to cranial therapies. The advent of Limoge Currents became the basis for the release of a Transcutaneous Electrical Nerve Stimulation (TENS) in 1974. Microcurrent Electrical Therapy (MET) was developed approximately in 1984, was incorporated into CES devices such as the Alpha-stim 100 (Limoge et. al., 1999; Kirsch, 2010). Another non-cranial therapy, ElectroAcupuncture, is indicated for local anesthesia in combination with anesthetic primers and combines EA (in this case local EA) and acupuncture (Christensen et. al., 1993).

3. Dosage

This section aims to further clarify the stimulation dose associated with select approaches. It is noteworthy that even early in transcranial electrical stimulation development it was recognized that 1) Stimulation waveform along with electrode positions (stimulation dose, Peterchev et. al., 2011) can be varied to change efficacy and safety; 2) the value of current controlled stimulation in contrast to voltage controlled stimulation; and 3) that electrode design including the use of a fluid/gel (electrolyte) buffer between the metal electrode and skin increases skin tolerability (Merrill et. al., 2005). None-the-less, ad hoc and often poorly documented variations in dose are coming in the literature, a matter that remains of concern to this date (Peterchev et. al., 2011). Unless otherwise stated, we presume that stimulation was current controlled.

Though we divide dose by category below, certain over-arching developments can be noted for both electrode design and waveforms. “Active” and “return” terminology for electrodes reflect only the brain target of interest with “active” being places nearer the target; evidently both electrodes will affect
brain function and indeed the position of the return determines "active" current flow (Bikson et. al., 2010). Early approach to stimulation the brain involved two "active" electrodes placed directly over the eyes with two "return" return electrodes, presumably to facilitate active current deliver through the optic foramina. Active electrode positions around the eye (e.g. supra-orbital) were explored, as well as reducing the number of active electrodes (e.g. single electrode on the forehead) or using just one return electrode. After 1970, approaches using electrodes on or around the ears were explored (though much earlier examples of ear electrodes are noted), with presumed current flow to deeper brain structures (Datta et. al., 2013). In the 1980's, approaches using tES showed that current could be delivered focally using small closely-spaced electrodes on the scalp (for example as indicated by motor responses). After 2000, contemporary approaches (e.g. tDCS, tACS...) used reduced currents and large-sponge electrodes (Nitsche and Paulus; 2000) with an "active" electrode placed 'over' the nominal target, though the use of larger electrodes and distant electrodes precludes focal stimulation (Datta et. al., 2009) of cortex or avoidance of deep brain structures (Dasilva et. al., 2012) though functional effects may be shaped (Nitsche et. al., 2007). Current approaches using arrays of small high-definition are intended to allow focal cranial stimulation.

In the context of waveform, a notable overarching progression was: 1) From basic waveforms (often limited to existing stimulation hardware), to increasingly complex and customized waveforms motivated by the perception that increased efficacy, safety, or tolerability was needed; 2) With complexity and (proprietary) uniqueness especially developed in commercial devices (e.g. CES); 3) Leading to a reversion to the most basic waveform after 2000, associated with a resurgence of clinical interest using standardized and defined approaches. Early intended uses focused on short-term effects motivated investigators to explore increased intensities (e.g. sleep, anesthesia), while interest in chronic diseases (e.g. depression) is consistent with efforts using reduced (well tolerated) current intensities and increasingly prolonged (repeated session) use.
3.1 Electrosleep and derivative techniques

The dosage for electrosleep has evolved since it first was investigated in 1902 (Gilula and Kirsch, 2005). Dosage used for electrosleep consisted of electrode placement over each eye and a return electrode over the mastoid, with a waveform consisting of 100 Hz pulses between 20-25 mA (Knutson, 1967). The pulse width was between 0.3 to 0.6 ms and stimulation duration lasted from 20 to 60 minutes (Knutson, 1967). In 1966, the name changed to CET and shortly afterward a new dosage was developed. Due to subject discomfort and the changing perception that penetration of current in to the brain (including deep brain structures) did not require placement of electrodes directly on top of the eyes (Brown, 1975; Richthofen and Mellor, 1979). Under this CET electrode montage, the stimulation waveform was pulsed at 30-100 Hz, pulse width of 1-2 ms, at 0.1-0.5 mA (Richthofen and Mellor, 1979). TCET was proposed as a new name for ES/CET but under this new nomenclature the dose for TCET was unchanged in regards to electrode placement or waveform (Brown, 1975).

A notable change in dosage occurred with the advent of NET and CES after 1970. In NET and CES, the number of electrodes was reduced from 3 to 2 (Net Device Corp.; Kirsch, 2010; Liss Body Stimulator). The electrode placement for NET was in the subjects’ ears (NET Device Corp. Information) - an approach later adopted by some CES devices with electrodes clipped onto the ears (Kirsch, 2010). The waveform used in NET, and also in some later CES devices, was 0.5–100 Hz stimulation at up to 600 µA over a period of 20 minutes (Kirsch, 2010; NET Device Corp. Information). The other variant for CES devices uses 2 electrodes placed on top of the forehead. The waveform for this variant of CES uses 15, 500 or 15000 Hz at 4 V with 50 ms pulses and “off” periods of 16.7 ms (Datta et. al., 2013; Liss Body Stimulator Manual(M); Liss Body Stimulator Manual(B)).
3.2 Electroanesthesia and derivative techniques

The dose for electroanesthesia evolved since the early 1900s. An early electrode placement for EA/EN consists of 4 electrodes with either 2 electrodes applied to each temple or to the bilateral frontal and occipital areas (Brown, 1975). There are a wide range of frequencies and current intensities that were evaluated. As noted, EA has been tested with pure DC requiring current approximately 40 mA to induce EA (Brown, 1975). Under AC-only conditions, the frequency ranged from 10–20 kHz with intensities approximately 10 mA; higher current intensities were claimed to be needed with higher frequencies and currents of 500 mA and frequencies around 200 kHz have been used. When biased by DC, AC frequencies typically remained in the same range with the AC component ranges from 2.5–5 mA with the DC component also ranging from 2.5–5 mA. In some instances waveforms with a high frequency "ON" periods were incorporated into TCES. TCES uses three electrodes rather than the four in EA; the electrodes are positioned with a single electrode between the eyebrows and two return electrodes on the retro-mastoid region (Brown, 1975). TCES waveform consists of frequency trains. The high frequency portion of the train is "ON" for 3-4 ms at 130-167 kHz and "OFF" for 8ms periods. The low frequency portion ("ON"/"OFF") was ~77–100 Hz and the overall waveform uses 200-350 mA with 30-35 V (Limoge et. al., 1999).

3.3 Transcranial Direct Current Stimulation / Transcranial Random Noise Stimulation / Transcranial Alternating Current Stimulation

Developed over the last decade, Transcranial Direct Current Stimulation (tDCS), Transcranial Random Noise Stimulation (tDCS), and Transcranial Alternating Current Stimulation (tACS) are three different distinct forms of "contemporary" tES as far as waveform, but all share the same approach to electrode number and shape. Though each applies a distinct waveform, in all cases the duration of
stimulation is typically 20 minutes with a peak current of a few mA. Conventionally, two electrodes are used with one positioned “over” the target region and the other elsewhere on the scalp (often the contralateral supraorbital region) or elsewhere on the body in an extra-cephalic location (Paulus, 2010; Antal et. al., 2008; Zaehle et.al., 2010). Electrodes are typically saline soaked sponge material wrapped around a conductive rubber electrode, though gel may also be used. In tDCS the (positive) anode and (negative) cathode are distinguished for their actions on cortical excitability- 1-2 mA is applied over 5-20 minutes (Paulus, 2010). For tACS, a single sinusoid at 10-40 Hz with a peak intensity of 0.4-1 mA has been tested (Antal et. al., 2008; Paulus, 2011; Zaehle et.al., 2010). The waveform parameter for tRNS includes: “a frequency spectrum between 0.1 Hz and 640 Hz...[and]... a normally distributed random level of current generated for every sample at a sampling rate of 1280 samples per second with no overall DC offset.”(Paulus, 2010; Chaieb et. al., 2009).

3.4 “Transcranial Electrical Stimulation”

“TES” uses high-intensity pulses (150-1840 Volts, presumed to be voltage controlled) lasting between 13-48 µsecs at an intermittent frequency of 1-3 seconds or less (Rossini et. al., 1985; Zentner et. al., 1989; Rothwell et. al., 1994; Kalkman et. al., 1992). Typically stimulation is applied using a bifocal (and bipolar) montage, but a “unifocal” montage has also been explored with an active electrode over the target a “ring” of return electrodes, either as a single band or 12 separate electrodes, around the width of the scalp (Rossini et. al., 1985; Rothwell et. al., 1994; Kalkman et. al., 1992).

3.5 Electroconvulsive Therapy

The waveforms for ECT are high-intensity, ~800 mA, with trains lasting 1-6 seconds per cycle. The electrodes are placed either unilaterally or bilaterally on the cranium and current intensity is typically increased by varying the number of pulses per train, pulse duration, or intensity until a seizure
is triggered (Gilula and Kirsch, 2005; Sackeim et. al., 2000). Modern efforts to refine dose has focused on minimized memory loss for example through focused stimulations (Spellman et. al., 2009; Datta et. al., 2008).

3.6 High Definition transcranial Direct Current Stimulation

HD-tDCS shares the same waveform with tDCS, 1-2 mA at 5-20 minutes, however the large sponge electrodes used for tDCS (as for tACS/trNS) are replaced with an array of smaller electrodes. The electrode montage is then optimized for brain targeting for example the 4x1-Ring montage uses a center electrode with determines the polarity of stimulation (anode or cathode) and four return electrodes at ~4-7 cm radius. More broadly, High-Definition Transcranial Electrical Stimulation (HD-tES) spans all efforts to focalize prior diffuse tES protocols by using arrays of HD electrodes to rationally guide current flow (Dmochowski et. al., 2011).

[INSERT TABLE 2 ABOUT HERE]
References


FDA Executive Summary. Prepared for the January 27-28, 2011 meeting of the Neurological Panel Meeting to discuss the Classification of Electroconvulsive Therapy Devices.


Liss Body Stimulator Manual(B), Bipolar Model No. SBL-502-B Manual. 480


NET Device Corp Information. About NET. http://www.netdevice.net/aboutnet.php


Figure 1: A general timeline of ES/EA noting key points in the history from 1902 until 2011 as well as their relation to DC stimulation. A brief history of DC stimulation is also presented in this table. Other cranial therapies are mentioned for a complete cranial stimulation history and non-cranial therapies are mentioned for their connection to ES/EA. Arrows are used to connect historically related points while the horizontal purple lines are used to point out DC use in historically pulsed applications.
Table 1: Dosages of the various cranial stimulation methods are shown. The year at which the form of stimulation came about is written with the stimulation method. Each method is connected to an electrode placement as well as a waveform used.
Table 2: Different classes of tPCS are summarized including temporal waveform (function), the associated magnitude spectrum (frequency content), and clinical references including dose using “CES”. The Fourier series were generated using the same parameters for $T$, $\tau$, and $A$ across all classes and the same parameters for $h$, $D_0$, $T_{on}$, and $T_{off}$ where applicable. Note $n$ is a discrete function of $1/T$ (or $T_{off}$ in the case of Class III). In Class III, the CES case would have $D_0$ set to zero which would lower the peak at zero. In Class II, $h_r = (h+1)/h$, in Class III, $T_r = T_{on}/T_{off}$ and in all classes, $P = A(\tau/T)$. The references indicated are:¹Limoge, Robert, Stanley 1999, ²Brown 1975, ³Bystritsky, Kerwin, Feusner 2008, ⁴http://www.net1device.com/specs.htm, ⁵Liss Stimulator Manual, Model No. SBL-502-B, ⁶Richthofen, Mellor 1979, ⁷Dimitrov, Ralev 2009, ⁸Liss Stimulator Manual, Model No.SBL-501-M. Adapted from Datta et. al., 2013.
<table>
<thead>
<tr>
<th>Waveform</th>
<th>Magnitude Spectrum</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I(A) - Monophasic Pulse</td>
<td>![Waveform Image]</td>
<td>-ES&lt;sup&gt;2&lt;/sup&gt; - CET&lt;sup&gt;5&lt;/sup&gt; - EA&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td>Class I(B) - Monophasic Pulse with DC offset</td>
<td>![Waveform Image]</td>
<td>-ES&lt;sup&gt;2,6&lt;/sup&gt; - LA&lt;sup&gt;2&lt;/sup&gt; - CFT&lt;sup&gt;2,6&lt;/sup&gt; - TCET&lt;sup&gt;5,2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Class II(A) - Biphasic Pulse</td>
<td>![Waveform Image]</td>
<td>-CES&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
<tr>
<td>Class II(B) - Biphasic Pulse with delay</td>
<td>![Waveform Image]</td>
<td>-TCET - Ces I - NFT&lt;sup&gt;4&lt;/sup&gt; - CES&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td>Class II(C) - Asymmetric Biphasic Pulse</td>
<td>![Waveform Image]</td>
<td>-CES&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td>Class II(D) - Asymmetric Biphasic Pulse with delay</td>
<td>![Waveform Image]</td>
<td>-CES&lt;sup&gt;5&lt;/sup&gt; - NET</td>
</tr>
<tr>
<td>Pulse Trains</td>
<td>![Waveform Image]</td>
<td>-LC&lt;sup&gt;1&lt;/sup&gt; - TCES&lt;sup&gt;1&lt;/sup&gt; - TF&lt;sup&gt;8&lt;/sup&gt;</td>
</tr>
<tr>
<td>Class I Train(50/55) (Ton/Toff)</td>
<td>![Waveform Image]</td>
<td>-LC&lt;sup&gt;1&lt;/sup&gt; - TCES&lt;sup&gt;1&lt;/sup&gt; - TF&lt;sup&gt;8&lt;/sup&gt;</td>
</tr>
</tbody>
</table>