Methods and Technologies for Low-Intensity Transcranial Electrical Stimulation: Waveforms, Terminology, and Historical Notes

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

Scope and Approach

Transcranial electrical stimulation (tES) encompasses all forms of research and clinical applications of electrical currents to the brain noninvasively 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 [1]. There has been a resurgence of interest since 2000, but "modern" tES developed incrementally over a century. This review provides the first comprehensive organization of approaches and doses 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 (Fig. 2.1).

1. Cranial electrical stimulation (CES) descended from electrosleep (ES) through cranial electro-stimulation therapy (CET), transcerebral electrotherapy (TCET), and neuroelectric therapy (NET).
2. Electroanesthesia (EA) 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 (IS).
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 the tES approach, typically employing basic, well-documented, and well-defined waveforms (e.g., one sinusoid [1] 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 tES 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 [2] which, in turn, gives rise to neurophysiological responses [3]; thus

B. Guleyupoglu (✉)
Department of Biomedical Engineering, The City College of New York, 160 Convent Avenue, 463 Steinman Hall, New York, NY 10031, USA
e-mail: bguleyup@gmail.com

P. Schestatsky
Department of Internal Medicine, Universidade Federal do Rio Grande do Sul, Capes, Brazil

F. Fregni
Department of Physical Medicine and Rehabilitation, Harvard Medical School, Berenson-Allen Center for Noninvasive Brain Stimulation, Boston, MA, USA

M. Bikson
Neural Engineering Laboratory, Department of Biomedical Engineering, The City College of New York of CUNY, New York, NY, USA

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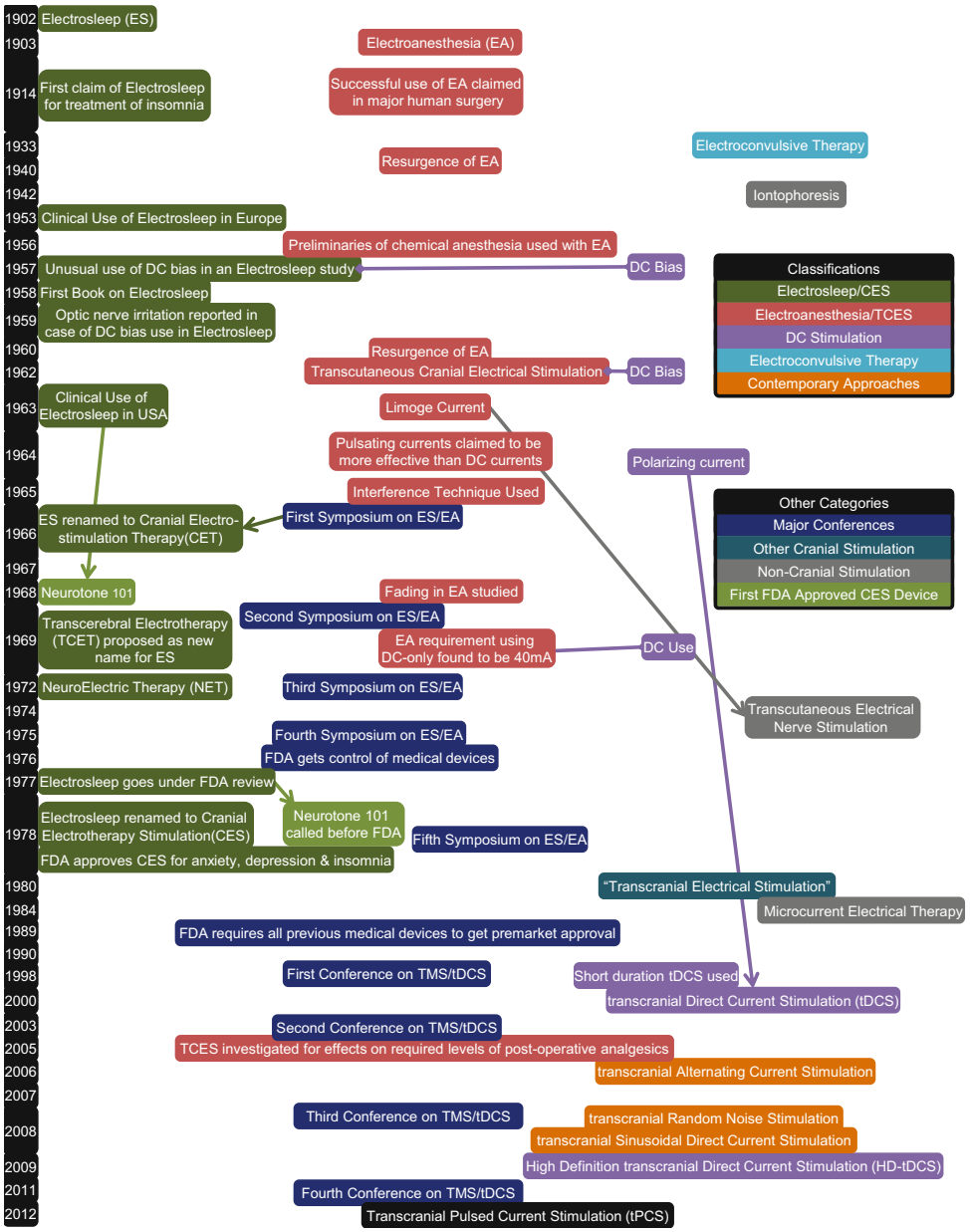

Fig. 2.1 A general timeline of ES/EA noting key points in the history from 1902 until 2011 as well as their relation to DC stimulation. A brief history of DC stimulation is also presented in this table. Other cranial therapies are mentioned for a complete cranial stimulation history and noncranial therapies 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

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 nonelectrical 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 (Figs. 2.2, 2.3, and 2.4). In addition, to promote a more comprehensive and systematic dose classification, we propose new categories for those waveforms using pulsed stimulation in Fig. 2.5 (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.

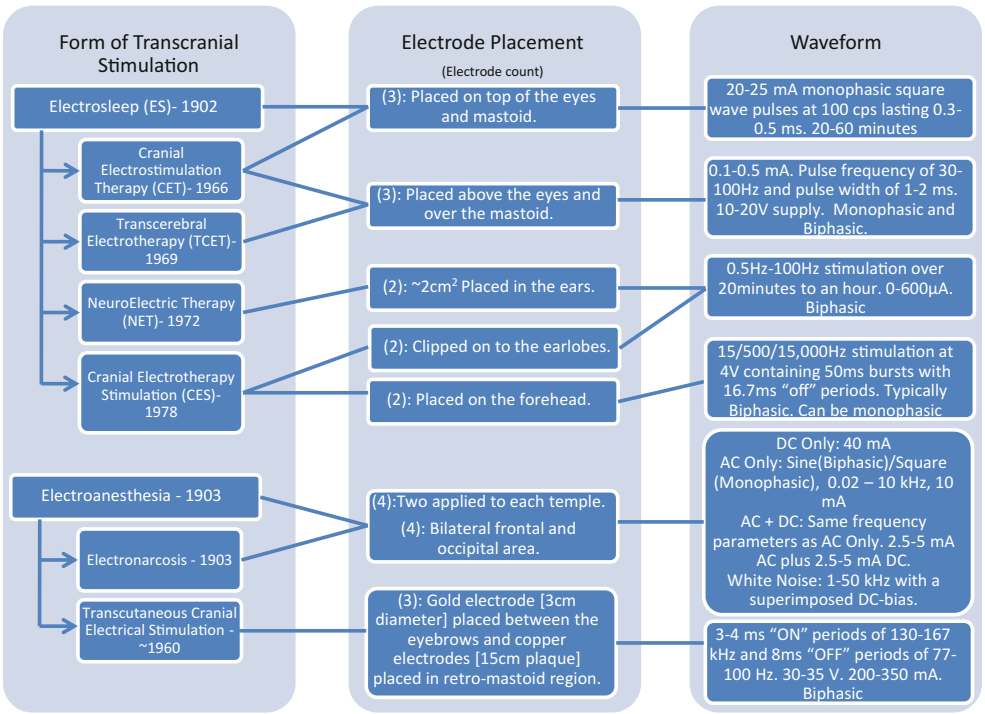

Fig. 2.2 Electrosleep and Electroanesthesia Dosage. These are a mixture of low- and high-intensity stimulation waveforms. The year at which the form of stimulation came about is written with the stimulation method. Each method is connected to an electrode placement as well as a waveform used

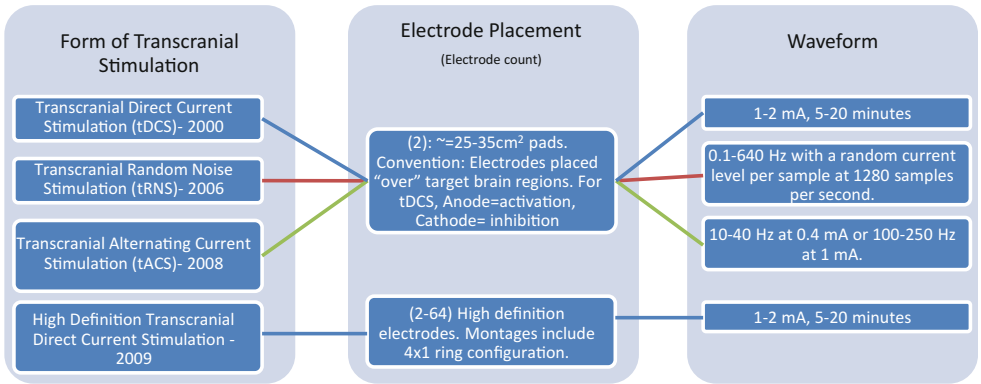

Fig. 2.3 Contemporary Approaches Dosages. These are primarily low-intensity stimulation waveforms. The year at which the form of stimulation came about is written with the stimulation method. Each method is connected to an electrode placement as well as a waveform used

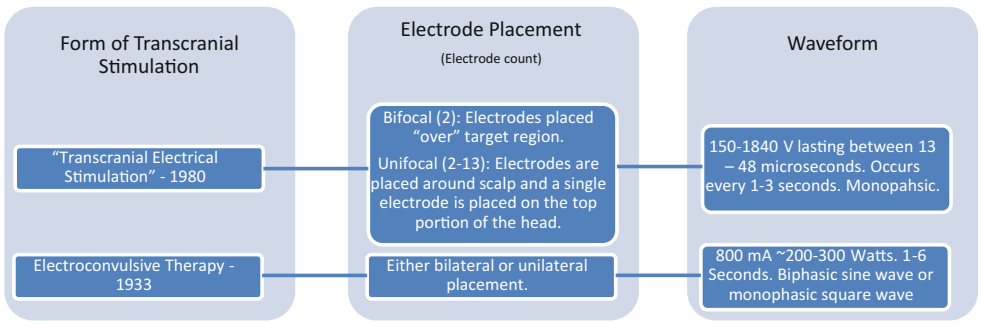

Fig. 2.4 "TES" and ECT Dosages. These are primarily high-intensity stimulation waveforms. The year at which the form of stimulation came about is written with the stimulation method. Each method is connected to an electrode placement as well as a waveform used

However, this ideal approach is problematic due to the following reasons: (1) In most cases, the complete dose details are not provided (e.g., electrode size, waveform details, etc.); (2) investigators often adjusted dose, resulting 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 ES use direct current (DC)?

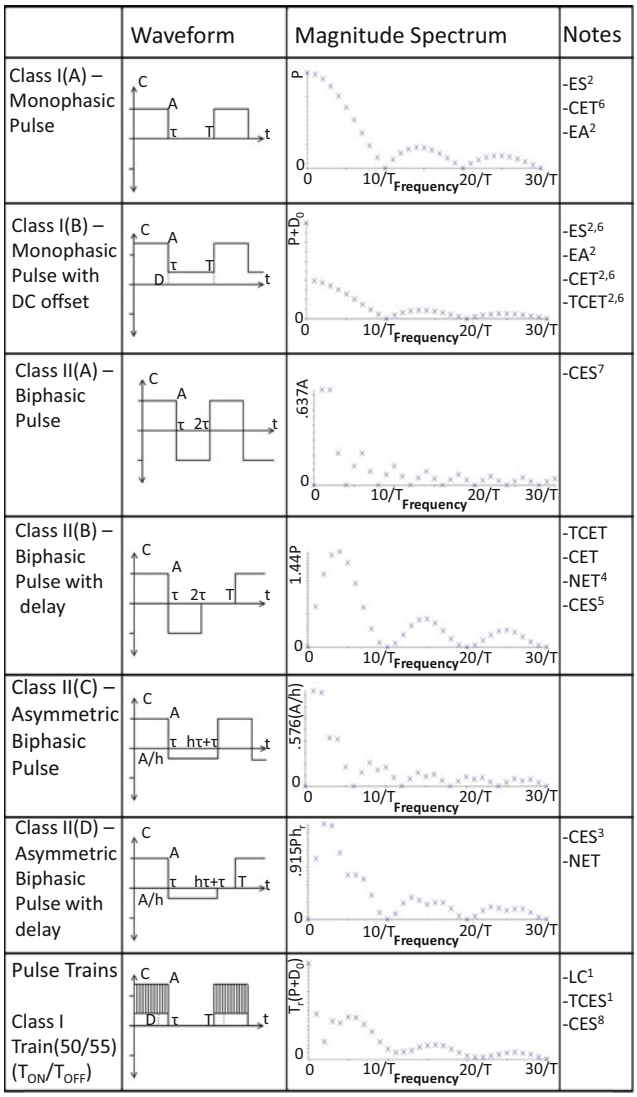

Fig. 2.5 Different classes of tPCS are summarized including temporal waveform (function), the associated magnitude spectrum (frequency content), and clinical references including dose using "CES." The Fourier series were generated using the same parameters for T, τ, and A across all classes and the same 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, $P = A(\tau/T)$. Data from [6, 13, 63]

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 [4]. 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.

Historical Development

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 ES were initiated in 1902 [5]; however, the first clinical report of ES was published 12 years later [6]. Most of the research regarding ES was conducted in Russia up until 1953, when clinical use of ES began in Europe [7]. 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 [6]. ES dose waveform was typically pulsed at 30–100 Hz, but at least one (unsuccessful) case of use of DC current was documented [6]. After 1963, an increased use of ES in the United States was noted. Three years later, the first symposium on ES and EA was held in Graz, Austria [7, 8]. At this symposium it was reasoned that ES does not actually induce sleep, rather it is an indirect side effect of the relaxing effects of stimulation. Therefore, the term *electrosleep* was changed to *cranial electrostimulation therapy* [8]. This was the first of several changes of the term "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 [6].

In 1969, TCET was proposed as another alternative name, which was adopted by the same authors [6]. In 1977, ES and its derivatives went under review by the US Food and Drug Administration (FDA) and in 1978 were classified as a Class III device for the treatment of Anxiety, Insomnia, and Depression [9]. However, such devices were renamed as *cranial electrotherapy stimulation* [10]. The FDA status of CES remains debated to the present day [9].

In 1972, a new method and device of ES called NeuroElectric Therapy (NET) [11, 12] 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 [10] and all subsequent CES devices approved by the FDA were through a 510 k 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 CES is thus a historical descendant of ES even as dose and indications have continuously evolved.

Developments from Electroanesthesia to Limoge Currents and Other Related Methods

Electroanesthesia, in short, was intended to induce anesthesia in the subject so that chemicals did not have to be used presurgery. EA studies started in 1903 but were first known as electronarcosis (EN) [6, 13]. Russian scientists used the term "electroanesthesia" to describe local anesthesia while "electronarcosis" described general anesthesia [6]. However, EA 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 [6, 14]. 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 [6]. 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 [15, 16]. 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 [6]" [16].

Research into EA dosage continued and the term *transcutaneous cranial electrical stimulation* 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" [13]. Even though the term TCES was not adopted until the early 1960s, similar protocols were used as early as 1902 by Leduc [13]. In 1951, Denier proposed that high-frequency trains of 90 kHz could be used to avoid muscular contraction [13]. 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 [13]. 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 [16]. In 1963, Aimé Limoge modified the TCES dose and called it *Limoge current* [13]. In 1964, a study claimed pulsating currents are more effective than direct currents for the induction of EA [6]. Another study suggested that the use of pure DC for EA required high intensity of approximately 40 mA [6].

In 1965, IS was proposed by Russian scientists and consisted of having two pairs of electrodes energized with sine waves of slightly shifted frequencies [6]. 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 (e.g., reduced pain, sensation, etc.) [6, 14]. 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 [3]) 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 [17] or increase in tolerability. In the first case, fading indicated a decrease in the subjects' anesthetic state while the dosage was kept steady [17]. Maintenance of anesthetic state was accomplished by either reduction of frequency or increase of current [17]. 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 postoperative analgesic requirements [18], as are other contemporary tES approaches [19].

Contemporary tES is also concerned with the treatment of a broad range of neuropsychiatric disorders, including pain [4, 20, 21]. Historically, EA/TCES used current intensities typically well above those used in contemporary tES. Nonetheless, 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.

Direct Current 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 alternating current (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 [6]. However, it was not until 1964 that preliminary studies heralding modern tDCS were published.

In 1964, Redfearn and Lippold investigated polarizing current for treatment of neuropsychiatric diseases [22], 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 [23]. Nitsche and Paulus established that prolonged tDCS could produce lasting and polarity-specific changes in cortical excitability [24] followed by pilot clinical studies [25]. Transcranial micropolarization is a technique investigated in Russia which is a modified version of tDCS using small electrodes instead of pads [26]. In 2007, HD-tDCS was proposed as a focalized form of tDCS [27]. HD-tDCS uses specially optimized electrodes [28], arranged in arrays that can be optimized per indication [29], including the 4 × 1 configuration [30].

Galvanic vestibular stimulation is being investigated for effects on ocular and postural movement [31]. 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 [32].

Electroconvulsive Therapy

Initially developed circa 1933, ECT [5, 33] used repetitive high-intensity pulses to trigger seizures. A common term 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 for CES). In 2011 the FDA summarized:

The ECT procedure was first conducted in 1938 [34]. Two Italian physicians, UgoCerletti and LucioBini, 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 [35]. They reported on the first treatment of a patient using this method in 1939 [36]. 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 1950s and 1960s, 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 United States declined [37]. However, in recent years, interest in, and use of, ECT has experienced resurgence; ECT use in the United States has been estimated at 100,000 individuals receiving this treatment annually [38]. Reflecting the greater proportion of women who suffer from major depression, two thirds of patients who receive ECT are women [39]. In clinical practice, ECT is generally considered after failure of one or more antidepressant medication trials, or when there is a 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, and Schizoaffective disorder. The evidence supporting the effectiveness of ECT for each of these indications is variable.

Contemporary Approaches

Two contemporary forms of tES are transcranial alternating current stimulation (tACS) and transcranial random noise stimulation (tRNS) [2]. Both tACS and tRNS use relatively low-intensity current and are being investigated for therapeutic effects [2]. A modified protocol for tACS is transcranial sinusoidal direct current stimulation (tSDCS) [40] 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 [41] 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 min after stage 2 sleep occurred for the first time, without reversion to stage 1, and stimulation continued at 5 min intervals with a 1 min break throughout the night [41].

Transcranial Alternating Current Stimulation

The first mention of "TES" was 1980 in a study by Morton and Merton [42]. "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 "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 [43–45]. 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 intraoperative evaluation in anesthetized subjects and "TES" was first "cleared" by the FDA in 2002 for monitoring.

Noncranial Therapies

Noncranial 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 transcutaneous electrical nerve stimulation (TENS) in 1974. Microcurrent electrical therapy (MET) was developed approximately in 1984 and was incorporated into CES devices such as the Alpha-stim 100 [10, 13]. Another noncranial therapy, electroacupuncture, is indicated for local anesthesia in combination with anesthetic primers and combines EA (in this case local EA) and acupuncture [46].

Dosage

This section aims to further clarify the stimulation dose associated with select approaches. It is noteworthy that even early in TES development it was recognized that: (1) stimulation waveform along with electrode positions (stimulation dose [1]) can be varied to change efficacy and safety; (2) the value of current controlled stimulation in contrast to voltage controlled stimulation; and (3) electrode design including the use of a fluid/gel (electrolyte) buffer between the metal electrode and skin increases skin tolerability [47]. Nonetheless, ad hoc and often poorly documented variations in dose are coming in the literature, a matter that remains of concern to this date [1]. Unless otherwise stated, we presume that stimulation was current controlled.

Though we divide dose by category below, certain overarching 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 [48]. 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., supraorbital) 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 [49]. In the 1980s, approaches using tES showed that current could be delivered focally using small closely spaced electrodes on the scalp (e.g., as indicated by motor responses). After 2000, contemporary approaches (e.g., tDCS, tACS, etc.) used reduced currents and large-sponge electrodes [24] with an "active" electrode placed "over" the nominal target, though the use of larger electrodes and distant electrodes precludes focal stimulation [27] of cortex or avoidance of deep brain structures [50] though functional effects may be shaped [51]. Current approaches using arrays of small high-definition electrodes 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, etc.), while interest in chronic diseases (e.g., depression) is consistent with efforts using reduced (well tolerated) current intensities and increasingly prolonged (repeated session) use (Fig. 2.1).

Electrosleep and Derivative Techniques

The dosage for ES has evolved since it first was investigated in 1902 [5]. Dosage used for ES consisted of electrode placement over each eye and a return electrode over the mastoid, with a waveform consisting of 100 Hz pulses between 20 and 25 mA [8]. The pulse width was between 0.3 and 0.6 ms and stimulation duration lasted from 20 to 60 min [8]. In 1966, the name changed to CET and shortly afterward a new dosage was developed. Due to patient discomfort and the changing perception that penetration of current into the brain (including deep brain structures) did not require placement of electrodes directly on top of the eyes [6, 52]. 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 [52]. 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 [6].

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 [10, 53, 54]. The electrode placement for NET was in the subjects' ears [53]—an approach later adopted by some CES devices with electrodes clipped onto the ears [10]. 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 min [10, 53]. The other

variant for CES devices uses two electrodes placed on top of the forehead. The waveform for this variant of CES uses 15, 500 or 15,000 Hz at 4 V with 50 ms pulses and "off" periods of 16.7 ms [49, 54, 55].

Electroanesthesia and Derivative Techniques

The dose for EA evolved since the early 1900s. An early electrode placement for EA/EN consists of four electrodes with either two electrodes applied to each temple or to the bilateral frontal and occipital areas [6]. 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 [6]. Under AC-only conditions, the frequency ranged from 10 to 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 to 5 mA with the DC component also ranging from 2.5 to 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 retromastoid region [6]. 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 8-ms periods. The low-frequency portion ("ON"/"OFF") was ~77–100 Hz and the overall waveform uses 200–350 mA with 30–35 V [13] (Fig. 2.3).

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

Developed over the last decade, tDCS, tRNS, and 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 min 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 [40, 56]). 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 min [2]. For tACS, a single sinusoid at 10–40 Hz with a peak intensity of 0.4–1 mA has been tested [2, 40, 56]. The waveform parameter for tRNS includes: "a frequency spectrum between 0.1 and 640 Hz... [and]... a normally distributed random level of current generated for every sample at a sampling rate of 1,280 samples per second with no overall DC offset." [2, 57].

High-Definition Transcranial Direct Current Stimulation

High-definition transcranial direct current stimulation shares the same waveform with tDCS, 1–2 mA at 5–20 min; 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 4 × 1-Ring montage uses a center electrode which determines the polarity of stimulation (anode or cathode) and four return electrodes at ~4–7 cm radius. More broadly, HD-tES spans all efforts to focalize prior diffuse tES protocols by using arrays of HD electrodes to rationally guide current flow [29] (Fig. 2.4).

Transcranial Electrical Stimulation

"Transcranial electrical stimulation" uses high-intensity pulses (150–1,840 V, presumed to be voltage controlled) lasting between 13 and 48 μs at an intermittent frequency of 1–3 s or less [43, 45, 58, 59]. 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 [45, 58, 59].

Electroconvulsive Therapy

The waveforms for ECT are high-intensity, ~800 mA, with trains lasting 1–6 s 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 [5, 60]. Modern efforts to refine dose have focused on minimizing memory loss, for example through focused stimulations [61, 62] (Fig. 2.5).

Conclusion

The field of electromedicine has evidently evolved through the past 100 years. Early technology evaluated very basic waveforms, continued on to increasingly complicated waveforms (i.e., pulse trains; *see* Fig. 2.5),

returning to more defined and simple waveforms at the turn of the century (i.e., tDCS and tACS). Although techniques and protocols have constantly been adjusted (with many waxing and waning in popularity), it is not prudent to globally conclude that early approaches were ineffective or that they should be automatically ignored; rather, both experience with efficacy (even when anecdotal or not fully documented by modern standard) as well as findings on safety (which were significant enough to warrant dose changes) should be considered to inform ongoing efforts. In this sense, the history on electrical stimulation may guide ongoing rational advancement.

Reporting the stimulation dosage used as well as the specific device used is and continues to be important for reproducibility. Descriptions of waveforms can at times be convoluted and we proposed ongoing efforts to carefully define the dosages and devices as well as using a form of standardized terminology (such as the one stated in Fig. 2.5) can be extremely useful in furthering research at a faster pace. The focus on terminology and dose in this review is intended to disambiguate the historical narrative, which is necessary if past experience with specific dose is to inform ongoing efforts.

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