

HELENA KNOTKOVA
RICARDO CRUCIANI
JOAV MERRICK
EDITORS

PAIN

BRAIN STIMULATION IN THE TREATMENT OF PAIN

Disability
Studies Series
Joav Merrick
(*Series Editor*)



NOVA

Pain
Brain stimulation in the
treatment of pain

Helena Knotkova, Ricardo A Cruciani and Joav Merrick

Disability studies book series

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FOREWORD

For both the scientific and the clinical communities, the excitement generated by translational research is proportionate to the complexity and generalizability of the science and the potential clinical payoff down the road. From this perspective, the work now being done to translate techniques of brain stimulation to the realm of pain management is exciting indeed.

The overarching scientific rationale of neurostimulatory therapies for pain—that CNS structures undergo neuroplastic changes in response to a variety of stimuli, that these changes can sustain disease states such as pain, and that stimulation of the nervous system using varied sources of energy has the potential to reset or remodel brain activity in a way that serves health—has been recognized for many decades. Although relatively little is known about the physiology and chemistry underlying the neuroplasticity involved in acute and chronic pain pathophysiology, or its reversal through treatment, the reality of these processes is now widely accepted. Functional neuroimaging, quantitative sensory testing, neurocognitive testing and other measures substantiate the remarkable shifts in neuronal activation that may occur and correlate with clinical phenomenology, including pain perception and analgesia. The science is inchoate, but the relevance to human experience and the accessibility to therapeutic intervention is recognized, and is the driver for translational research of enormous promise.

Clinical applications of stimulation have been explored at every level of the neuraxis, from the cutaneous afferents to peripheral nerve, and from spinal cord to brain. Deep brain stimulation and cortical stimulation have been commercialized and are used ‘off-label’ by a small number of pain specialists who have familiarity with the approaches and access to the expertise to undertake them. In an analysis of risk and benefit, they typically are viewed as among the “last resort” measures for chronic pain, a perspective justified by the limited data (and no evidence of comparative effectiveness) and the risk inherent in neurosurgery.

The advent of transcranial stimulation techniques shifts the risk-to-benefit analysis and potentially opens the door to widely expanded trials of central neurostimulation therapies for pain. The research now ongoing can accelerate if the delivery approach to stimulation is non-invasive. Future studies can target localization parameters for stimulation, timing strategies, pharmacologic augmentative effects, clinical predictors of efficacy and a range of other questions. If transcranial approaches prove to be safe and effective, they could change the current view of best practice in pain management and assume a significant role in the clinic. With thoughtful, targeted translational research, this potential can be assessed relatively soon.

This volume provides the background on brain stimulation for pain and an unique update on the status of transcranial stimulation. The Editors deserve great praise for bringing together an international group of basic and clinical scientists, each of whom is a leader in advancing the development of this work. The volume may be a milestone on a path that eventuates in broad uptake of new therapies in the clinic. It certainly supports an expanded research agenda for brain stimulation, and particularly transcranial stimulation in pain management.

Russell K Portenoy, MD

Chairman and Gerald J and Dorothy R Friedman Chair in Pain Medicine and Palliative Care

Professor of Neurology and Anesthesiology

Albert Einstein College of Medicine

Department of Pain Medicine and Palliative Care

Beth Israel Medical Center

First Avenue at 16th Street

New York, NY 10003

Telephone: 212 844-1505

Fax: 212 844-1503

E-mail: RPortenoy@chpnet.org

INTRODUCTION

Ricardo A Cruciani, MD, PhD^{*1,2,3}, Helena Knotkova, PhD^{1,2} and Joav Merrick, MD, MMedSci, DMSc^{4,5}

¹Institute for Non-invasive Brain Stimulation of New York, Research Division, Department of Pain Medicine and Palliative Care, New York

²Department of Neurology, Albert Einstein College of Medicine, Bronx, New York

³Department of Anesthesiology, Albert Einstein College of Medicine, Bronx, New York, United States of America

⁴National Institute of Child Health and Human Development, Office of the Medical Director, Division for Mental Retardation, Ministry of Social Affairs, Jerusalem, Israel

⁵Kentucky Children's Hospital, University of Kentucky, Lexington, United States

Recent surveys suggested that chronic pain affected as many as 3% of the worldwide population and there is an evidence that chronic pain patients are twice as likely to commit suicide as compared with the healthy population. It should also be remembered that the lifetime prevalence of suicide attempts in the chronic pain population is about 10%. Although various innovative pharmacological preparations and formulas have been implemented into clinical practice in recent years, chronic pain in many patients have not been successfully maintained at an acceptable level, thus not allowing the patients to resume their life-activities.

* Correspondence: Ricardo A. Cruciani, MD, PhD, Department of Pain Medicine and Palliative Care, 1st Ave at 17th Str., Baird Hall, 12th fl, New York, NY, 10003, United States. E-mail: RCrucian@chpnet.org

Despite remarkable advances in pain management, chronic pain remains under-treated, depicting the need for new therapeutic approaches in chronic pain.

In the past years, neuroimaging techniques provided a better insight into mechanisms involved in the development and maintenance of chronic pain. Chronic pain does not develop as a simple direct result of activity in nociceptive fibers following a traumatic event, but rather represents a consequence of dynamic plastic changes in sensory, affective and cognitive systems and related neuronal networks. The functional neural changes associated with pain include both adaptive compensatory changes, as well as maladaptive changes that may contribute to dysfunction of involved anatomical and physiological systems. In accordance, research findings indicated that patients with some chronic pain syndromes developed functional reorganization of certain brain structures (for example in somatosensory- or motor cortices). Since research studies have shown that reversal of pathological cortical changes in chronic-pain patients is accompanied by pain relief, a modulation of brain excitability seems to be a promising approach to address pain related to central hyperexcitability. Brain stimulation techniques aim to selectively enhance adaptive patterns of neural activity, suppress the maladaptive ones, and restore the balance in disturbed neuronal networks.

In the past decades, numerous experimental studies in animals demonstrated strong inhibitory effects that electrical stimulation of nervous system can exert on nociceptive transmission. The encouraging findings from animal studies facilitated interest in the use of neurostimulation to induce pain relief in humans. The neurostimulation has mostly targeted the sensory pathways mediating transmission of non-noxious information (large afferent peripheral fibers, spinal dorsal columns or thalamic sensory nuclei), and to a lesser degree brainstem structures exerting anti-nociceptive influences (e.g. the peri-aqueductal or periventricular grey matter). In the 1950s, stimulation of sub-cortical motor fibers was shown to inhibit afferent transmission in the dorsal horns, later followed by findings on analgesic effect of motor stimulation. However, the use of motor cortex stimulation for pain control was not reported until the 1990s. Since then, MCS (motor cortex stimulation) has been used in selected chronic-pain populations to manage pain refractory to conventional pharmacological approaches.

In the past two decades, non-invasive alternatives to MCS, transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) have been developed. Both TMS and tDCS have been studied in healthy volunteers, patients with various disorders, as well as in a variety of pain syndromes. Up to date, multiple reports on TMS have shown that repetitive TMS

at higher operating frequencies can efficiently alleviate pain, indicating clinical potential of this technique. Recently, both research and technical innovative initiatives have addressed the predominant obstacles (high initial, operating and maintenance costs, and advanced level of skills required to operate the unit) that prevented TMS from broader implementation into routine pain management, and there is a hope that in coming years, TMS will be utilized in pain practice to its full potential.

In comparison with TMS, tDCS has been developed more recently, and thus less evidence from controlled studies is available on analgesic efficacy of tDCS. However, the exiting research findings together with empirical observations suggest a great potential of tDCS to serve as a therapeutic tool in management of chronic neuropathic pain.

In conclusion, the findings collected in the past decade open exciting perspectives for clinical application of brain stimulation techniques in pain management, at least for selected populations of patients suffering chronic pain resistant to conventional therapy. Beyond this therapeutic purpose, both invasive and non-invasive brain-stimulation approaches can help to further explore relationship between cortical plasticity and pain.

Chapter 1

INTRODUCTION TO ELECTROTHERAPY TECHNOLOGY

***Marom Bikson*, PhD, Abhishek Datta, MS,
Maged Elwassif, MS, Varun Bansal and
Angel V Peterchev, PhD***

Department of Biomedical Engineering, City College of New York of CUNY,
New York and Division of Brain Stimulation and Therapeutic Modulation,
Department of Psychiatry, Columbia University, New York,
United States of America

Electrotherapy involves electric or magnetic stimulation of the human body in a range of therapeutic applications including pain alleviation. A wide spectrum of electrotherapy paradigms have been deployed in pain treatment, illustrating the inherent flexibility of this technology, but also the fundamental challenge of determining an optimal strategy. The effective and safe application of electrotherapy requires an understanding of the basic components of electrotherapy technology, as well as how to control electrotherapy dose. These topics are introduced in this review, along with related comments on the general mechanisms of electrotherapy, as well as an overview of various electrotherapy paradigms.

* Correspondence: Marom Bikson, PhD, Department of Biomedical Engineering, City College of New York of CUNY, T-403B Steinman Hall, 160 Convent Avenue, New York, NY 10031 United States. E-mail: bikson@ccny.cuny.edu

INTRODUCTION

Electrotherapy is the application of electricity to the human body for therapeutic purposes, including the alleviation of acute or chronic pain states. Here we briefly introduce the basic technology of electrotherapy, as it relates to practical decisions made by clinicians in determining a therapeutic strategy. A basic understanding of electrotherapy technology must inform effective and safe clinical treatment, and is therefore important for all practitioners of electrotherapy.

ELECTROTHERAPY DEVICE COMPONENTS

It is convenient to understand electrotherapy devices, including implanted and non-invasive (surface) devices, as made out of only two distinct functional components with additional support accessories. The first functional component is the stimulator device which generates the electrical signal. What electrical signal is generated is selectable by the operator from a set provided by the manufacturer. How this electrical signal changes over time is called the waveform of the electrical signal and can be described by features such as pulse shape, width, amplitude, polarity and frequency. The second functional component of electrotherapy devices are the electrodes. An electrode is where the metal conductor contacts the tissue or skin; for skin stimulation a sponge or gel may be placed between the metal and skin. At the electrodes, the electrical signal generated by the stimulator enters and then exits the body; for this reason there must always be at least two electrodes. The user positions the electrodes near the direct target of stimulation. For implanted devices, the stimulator device casing can serve as one electrode.

Whereas for non-invasive devices the stimulation waveform is adjusted by controls (e.g., knobs or keyboard) directly on the stimulator device, for implanted stimulation systems a telemetry system is used to adjust the stimulation waveform. Some devices use measurements from sensors, such as electrical potential recordings, to change stimulation waveform in real time using automatic feedback control.

Most electrical stimulator devices are either voltage-controlled or current-controlled. In a voltage-controlled device, the user specifies peak device output in units of volts, and the voltage output waveform of the device is regulated. For current-controlled devices, the user specifies peak device output in units of amperes, and the current output waveform of the device is regulated. However, all

stimulators output both a voltage and a current. For example, a current-controlled device changes its output voltage to achieve a desired current level. Finally, it should be noted that the voltage and current waveforms do *not* necessarily have the same shape, due to capacitive behavior of tissues and the electrode-tissue interface (1). Indeed, a concern with voltage controlled stimulation is that the current reaching the brain will be distorted from the programmed waveform. Though current controlled devices are thus generally preferred, technical or logistical factors result in many voltage controlled devices still being employed.

For magnetic stimulation, the electrodes are replaced with coils that are positioned on the body over the direct target. It appears that pulsed magnetic fields are not therapeutic in themselves, but rather, the magnetic fields produce tissue stimulation by inducing electrical currents in the body. Therefore, we consider electrotherapy inclusive of pulsed magnetic therapy. Analogously to electrical stimulation, in magnetic therapy, the electrical signal generated by the stimulator determines the waveform of the electrical currents in the body. However, unlike electrical stimulation, in magnetic stimulation there is no current entering or exiting the body. Rather, the electric currents induced by the magnetic field circulate within the body.

Additional hardware of electrotherapy devices can be considered accessories which largely serve mechanical and safety purposes rather than directly determine therapeutic efficacy. For example, for convenience the stimulator is often at some distance from the electrodes or magnetic coil, therefore insulated wires connect the stimulator to the electrodes/coil. The non-conducting mechanical support around implanted electrodes is referred to as leads. Surface electrode accessories may include some form of position support (adhesive, cap, or straps). For high intensity TMS, accessories such as air compressors, and water or oil circulation systems are sometimes used to cool the coil. Still additional accessories are used to position electrodes during implantation or around the cranium, as well as calibrate device output. Finally, all electrotherapy devices need a power source such as a battery or a line-connected power supply.

ELECTROTHERAPY PARADIGM CLASSIFICATION

A number of electrotherapy devices and paradigms have been introduced over the years and given names that are generally descriptive of the electrode or coil positions and/or the stimulation waveforms. Some examples of electrotherapy paradigms for cranial stimulation are illustrated in figure 1. For instance, Transcutaneous Electrical Nerve Stimulation (TENS) refers to electrical therapy

with superficial skin electrodes placed anywhere on the body including the cranium, with stimulation waveform consisting of repeated pulses (2-4). Electroacupuncture is similar to TENS, but uses needle electrodes that penetrate the skin (5). If one or more electrodes, or the stimulating coil, is placed on the head to target the brain, the stimulation paradigm is typically referred to as “transcranial” or “cranial”, such as in Transcranial Electrical Stimulation (TES) (6-8). Though TES can be applied with any waveform, “TES” has historically been used to specify high-intensity pulsed stimulation. Separate applications of TES include transcranial Direct Current Stimulation (tDCS) which employs superficial skin electrodes, with at least one placed on the cranium, and a stimulation waveform that is direct current (DC) (9-11). The same electrode configurations can be used with alternating currents—transcranial alternating current stimulation (tACS) (12). Similarly, Cranial Electrical (or Electrotherapy) Stimulation (CES) uses superficial cranial electrodes, but the stimulation signals are square waves modulated at various frequencies (13). High-density Transcranial Electrical Stimulation (HD-TES) incorporates arrays of surface cranial electrodes to increase focality (14). High-density transcranial Direct Current Stimulation (HD-tDCS) similarly employs arrays of cranial electrodes and uses DC current.

For more targeted and chronic stimulation, the electrodes can be implanted intracranially. For example, Deep Brain Stimulation (DBS) employs electrodes implanted proximal to deep brain structures, and stimulation with pulse trains (15). A less invasive form of intracranial stimulation uses epidural or subdural electrodes to stimulate a specific superficial cortical area such as motor cortex (e.g., epidural cortical stimulation (ECS), motor cortex stimulation (MCS)) (16-18). Implanted electrodes can also be used for chronic extracranial nerve stimulation. For example, Vagus Nerve Stimulation (VNS) and Spinal Cord Stimulation (SCS) involve chronic stimulation with electrodes implanted around the vagus nerve and the spinal cord, respectively (19-22).

Finally, electrical stimulation can also be induced by pulsed magnetic fields. Transcranial Magnetic Stimulation (TMS) encompasses treatments using a magnetic stimulation coil placed over the head inducing brief electrical current pulses in the brain (6,18). TMS has the advantage that it produces less scalp discomfort than suprathreshold TES, and is therefore more tolerable in unanesthetized subjects. Therapeutic TMS applications typically apply stimulation with pulse trains (repetitive TMS (rTMS)). Low-frequency rTMS is administered in continuous trains at 0.2-1 Hz, whereas high-frequency rTMS is administered as intermittent pulse trains of 5-20 Hz (18). A number of novel TMS paradigms that aim to increase the neuromodulatory effectiveness and selectivity of rTMS have been introduced recently, including theta burst stimulation (TBS), repetitive

monophasic pulse stimulation, paired- and quadri-pulse stimulation, paired associative stimulation, controllable pulse shape TMS (cTMS), and deep-brain TMS (12).

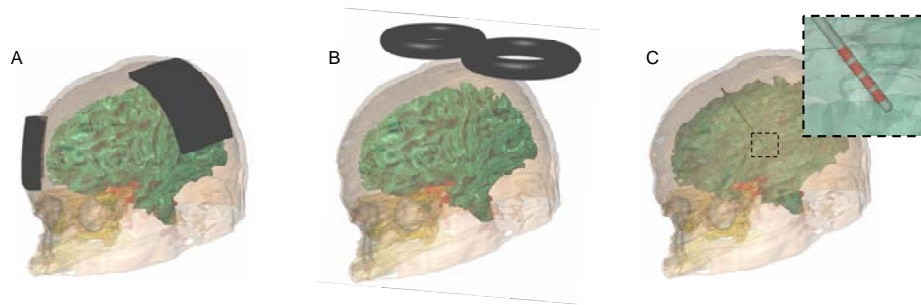


Figure 1. Illustration of some brain stimulation paradigms. Stimulation with surface electrodes is called transcutaneous stimulation. When the electrodes are placed on the scalp to target the brain, the paradigm is referred to as cranial or transcranial stimulation (A). Magnetic stimulation employs coils of wire wound in specific patterns (e.g., “figure of 8”). When the coil is positioned on the head, the paradigm is called Transcranial Magnetic Stimulation (TMS) (B). Electrotherapies using implanted electrodes are generally classified by the target anatomical structure near the electrodes such as Spinal Cord Stimulation, Vagus Nerve Stimulation, or Deep Brain Stimulation (C)

The above examples indicate that the electrotherapy paradigm classification usually involves a description of the electrodes/coil position and/or the stimulation waveform generated. It should be emphasized that each of these classifications typically covers a wide parameter set. For example, TENS encompasses a range of stimulation amplitudes and frequencies (4,23). Moreover, simply because two distinct electrotherapies fall under the same umbrella classification does not mean that those therapies share a common mechanism of action or therapeutic outcome. This point is particularly important from the perspective of controlling and reproducing electrotherapy dose. For example, the fact that two medical devices share the same label (e.g., TENS) does not mean that they generate stimulation with identical parameters. Therefore, indicating only the therapy classification (e.g., TENS) in a report does not provide enough information for the therapy to be reproduced. Rather, it is necessary to fully account for and report the electrode or coil type and positions, and the stimulator waveform parameters (pulse shape, width, amplitude, polarity, frequency, train duration, etc.). Typically, the stimulation paradigm can be fully described by providing the manufacturer name and a unique model or part number (P/N) of the

stimulator device and the electrodes or coil, as well as the settings of the user-selectable stimulation parameters used in the treatment.

In summary, from the perspective of therapeutic efficacy, what makes each electrical therapy different is 1) the waveform generated by the stimulator, and 2) the electrodes/coil type and location. Thus, when considering an appropriate electrical therapy, the decisions that a clinician must make can be conceptually reduced to selecting electrode/coil types and positions, and the stimulation waveform characteristics (24). The former can be conceived of as spatial targeting of the stimulation, whereas the latter amounts to controlling the temporal dynamics of the stimulation.

RATIONAL ELECTROTHERAPY DESIGN

The combination of electrode/coil type and positions, and stimulator output waveform determine electrotherapy dose. Clinicians must integrate both factors together in determining an electrotherapy strategy, however, it is also useful to conceptually consider each independently. As emphasized above, clinicians must fully account for and report stimulation dose for therapies to be reproducible (24). When stimulation is administered repeatedly, the dose may change between sessions, for example, as the clinician optimizes stimulation parameters. Any changes of the electrotherapy dose during the course of treatment should be accounted for and reported as well.

The decision of where to place the electrodes or the coil is pivotal to electrotherapy outcome. Neuronal tissue near the electrodes/coil will be preferentially directly activated by stimulation. When considering the focality of electrical stimulation, to a first approximation, one can picture current entering the tissue at one electrode and travelling in a diffuse line toward the other electrode. Thus, the further apart the electrodes are, the longer and more diffuse the tissue region of current flow is. This is one reason why two closely implanted electrodes may generate more focal stimulation, compared to two surface electrodes on opposite sides of the head. For magnetic stimulation, the induced electrical currents follow roughly the shape of the stimulation coil. For example, a circular TMS coil will induce circular currents under the circumference of the coil. In this manner, one can grossly estimate where in the brain or peripheral nerves the current will flow, based on electrode/coil type and position.

There has been a continued effort to make the spatial targeting and dosing of stimulation paradigms more precise. For example, DBS electrodes are implanted using stereotactic guidance systems (25) and TMS applications are increasingly

adopting stereotactic coil positioning based on individual MRI and fMRI scans (26). Further, recent technical innovations in stimulation hardware are aiming to improve spatial targeting as well. For example the use of “ring” electrode configurations in High-Density Transcranial Electrical Stimulation is intended to enhance the focality of non-invasive cortical stimulation (27). Finally, setting of stimulation intensity relative to the subject’s response threshold is frequently used to individualize the treatment dose, exemplified by the rTMS dose adjustment relative to the motor evoked potential (MEP) threshold (28).

The region of the brain or the peripheral nervous system where the stimulation current is flowing is directly affected by the electricity. The cells in the targeted region will be exposed to electricity and as a result their function may change. The waveform of the electrical currents experienced by the cells depends on the waveform generated by the stimulator. The decision of what waveform to apply is complicated for a number of interrelated reasons. First, the ability to design rational electrotherapies is limited by our incomplete understanding of brain function and the mechanisms leading to pathology. Second, the interaction of electricity with neural tissue is complex. Third, there is a very large set of possible stimulation paradigms, thus empirical determination of an optimal configuration for a particular application is daunting. Finally, inter-individual and intra-individual variability of response to stimulation often precludes effective use of a standard dose in all patients at all stimulation sessions, requiring steps to individualize the treatment.

Regions of the brain that are functionally connected to the direct target of stimulation may be indirectly modulated by electrical and magnetic stimulation. For example, cortical stimulation may activate, inhibit, or otherwise modulate activity of various cortico-subcortical networks (18). Electrotherapies with direct targets in the peripheral nervous system, such as VNS, are particularly based on indirect actions.

The cells in the nervous system (neurons) use electrical signals to process and transmit information. Because the nervous system is an electrical organ, it is sensitive to electricity. At the cellular level, the effect of applied electricity can be considered on three inter-related scales (see figure 2). First, the stimulating electrical currents may change the electrical state of the neurons (e.g., triggering of action potentials or blocking of firing). Second, changes in neuronal electrical state may lead to changes in neuromodulator or neurotransmitter activity (e.g., endogenous opioids and GABA). Third, the electrical activity on a network of neurons may be concomitantly altered (e.g., brain oscillations and gate control). To be therapeutically relevant, these electrical and chemical changes at cellular and network level must manifest as changes in behavior and/or cognition. Various

basic cellular mechanisms of electrical stimulation have been elucidated (1,29-32), however, relating cellular modulation to behavioral or cognitive changes remains a fundamental challenge. As a result, clinical determination of electrotherapy dose is currently driven largely by empirical considerations and patient-specific titration.

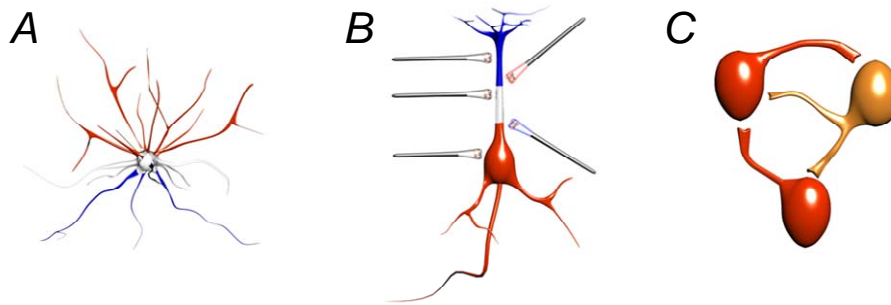


Figure 2. Schematic of the various levels of neural modulation induced by electrical stimulation. A) Individual neurons process information through changes in trans-membrane electrical potentials, including action potentials in axons. Applied electrical stimulation will modulate the electrical properties of single cells. B) Neuronal communication at synapses is itself an electrically driven phenomenon which will be modulated by applied electricity. C) Groups of neurons organize in neuronal networks which often generate coherent electrical signals such as electric fields oscillations (e.g. gamma oscillations). This network electrical activity may be modulated by applied electricity. The effects of applied electricity on single neurons, neurotransmitters, and neuronal networks can be quantified with biomarkers and in animal studies. However, relating these cellular and network level changes to complex behavioral and cognitive outcomes remains a fundamental challenge toward developing rational electrotherapy paradigms.

Due to the complexity and heterogeneity of strategies for empirical determination of electrotherapy dose, we limit ourselves to some general cautions here. First, the therapeutic/behavioral outcome of electrotherapy is not necessarily a monotonic function of any waveform parameter. For example, increasing stimulation frequency may first increase efficacy while further frequency increase may reduce efficacy. Nor is it necessarily possible to optimize each waveform parameter independently. For example, at stimulation frequency X the optimal amplitude may be determined as A, but at frequency Y the optimal amplitude may be B. Further, it is important to distinguish the acute (during stimulation) and plastic (lasting after stimulation) outcomes of stimulation. It is not necessarily the case

that an electrotherapy optimized for acute changes will be similarly effective for plastic change, and vice versa.

Inter-individual variability relates to difference in anatomy, physiology, and disease etiology across individuals that may fundamentally affect stimulation outcomes. For example, pain can arise from a myriad of tissues and be transmitted through distinct neurological pathways. Because of inter-individual variability, the same stimulation dose applied to two patients may have fundamentally different outcomes (33,34). Intra-individual variability relates to the dependence of electrotherapy on the current physiological state on the patient, including physical and mental states. For this reason, it may be necessary to adjust dose for the same patient across sessions or as the patient's response to stimulation changes.

For practitioners optimizing electrotherapy dose, there is generally a large set of possible parameter settings within the limits of each commercial device, in combination with an infinite set of possible electrode and coil positions. This flexibility should not be viewed as a limitation of electrotherapy, compared to, for example, pharmacological approaches where dosing is limited to far fewer parameters. The ability to change stimulation parameters (e.g., by the turn of a knob) and then iteratively optimize therapy in a patient-specific manner is a fundamental advantage of electrotherapy.

SAFETY OF ELECTROTHERAPY

As with any therapeutic approach, in selecting electrotherapy technology and dose, safety and efficacy considerations must often be balanced. For example, the use of implanted electrodes allows focal stimulation of regions inaccessible with surface electrodes, but is associated with potential surgical complications. Surface electrodes and coils are non-invasive, but are at some distance from the target, resulting in less focal stimulation that could induce unintended modulation of regions around the target.

In the context of waveform selection, commercial stimulation devices generally add safety features such as the limitations of stimulation intensity, ramping on/off of stimulation intensity, or automatic waveform controls such as the use of charge-balanced pulses. These limits are generally predetermined by the manufacturer and are not necessarily apparent to the clinician programming the device. However, even though automatic waveform changes may not be transparent to the clinician, they may still impact efficacy.

Electrotherapy within safety guidelines established by clinicians and manufacturers is generally well tolerated in the majority of patients (28,35).

None-the-less, fundamental unknowns about the reaction of tissue to electrical stimulation, combined with the desire by clinicians to explore new stimulation targets and protocols, warrants continued vigilance on the part of clinicians and researchers. There are specific safety concerns for each technology. For example, seizure risk is the major safety concern in rTMS (28). On the other hand, electrochemical damage is not a factor in TMS, whereas it is of paramount concern for stimulation with implanted electrodes. Moreover, there are distinct safety concerns for voltage-controlled and current-controlled stimulation (1). Both potential tissue damage, and cognitive or behavioral changes induced by stimulation need to be addressed for each stimulation technology and dose. Even for some FDA approved treatments, there are lingering and emerging concerns about potential damage of tissue during normal operation and under unexpected conditions (36,37).

CONCLUSIONS

Electric and magnetic stimulation (electrotherapy) can confer therapeutic benefit by inducing electrical currents in neural tissue. Electrotherapy paradigms can be conceptually reduced to two functional components: 1) electrode or coil type and position, and 2) stimulation waveform. Stimulation paradigms are often broadly classified based on the electrode/coil location and/or waveform parameters. Reproducible electrotherapy requires rational control and documentation of electrical dose. For each electrotherapy technology, there is a balance of efficacy and safety factors. Basic knowledge of the biophysics of neural stimulation is necessary for rational determination of electrotherapy dose, however, the present lack of full understanding of the mechanisms of electrotherapy necessitates empirical optimization of treatment dose. For this reason, we expect that the full potential of electrotherapy has yet to be realized. Basic research on the mechanisms of electrotherapy may thus manifestly improve electrotherapy outcomes. For in-depth discussions of electrotherapy mechanisms, safety, and applications we refer the reader to more specialized literature reviews (6,28,38) and to the other chapters in this book.

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