NEXALIN TECHNOLOGY

The Future of Healthcare

Setting The Standard In Cranial Electrical Stimulation

For More Information Visit:
NexalinTechnology.com
How Nexalin Therapy Works

Brain Stimulation Using Nexalin Technology:
A Non-Invasive Method of Treating Anxiety, Depression, and Insomnia

Dr. Yakov Katsnelson and Raymond Pizinger
March 16, 2008

Nexalin Advanced Therapy Centers, LLC's
SYNOPSIS

The human brain is the most complex organ in the body and is constantly changing, making it difficult for science to know exactly how it works. Although we have very strong opinions about it, the exact mechanism by which Nexalin® Advanced Therapy produces such positive results is not fully understood. However, laboratory and clinical evidence suggest that Nexalin's patented electrical stimulation affects the hypothalamus and related brain structures to adapt and change the levels of neurochemicals including neuropeptides, neurotransmitters and neuromodulators. The data support that the Nexalin electrical stimulation results in the endocrine outputs moving toward “normalization,” specifically those coming from the hypothalamic nuclei and associated brain structures. A key indicator of this is a significant clinical change in levels of enkephalins and beta-endorphins in the cerebral spinal fluid of Nexalin treated subjects, as well as other neurochemicals like serotonin. The change in these neurochemicals is also apparent based on the responses noted by the patients after they receive Nexalin Advanced Therapy.

The hypothalamus’ main function is to maintain homeostasis (state of equilibrium) of the body. In order to perform this function, it is constantly sensing and adapting to information received by the brain. So, by nature the hypothalamus is sensitive and responsive to stimuli. Many disorders including depression, anxiety, and insomnia are believed to be a result of a decrease in the production of specific neurochemicals. Pharmaceutical therapies act by replacing these neurochemicals with a drug; Nexalin Therapy works by permitting your body to manage the production of these neurochemicals on its own. With its regimen of consecutive treatment sessions, Nexalin Therapy utilizes the hypothalamus’ adaptive ability resulting in changes in the production of these neurochemicals to more normalized levels. The clinical effect is a decrease in the symptoms. Clinical trial results confirm these results, as illustrated in Figures 3 & 4, where the clinical effect maintains its statistical significance through the 12-week follow up period.

The Nexalin device has extensive clinical experience; the clinical trials have studies more than 700 subjects and provided more than 10,000 therapies. Nexalin Therapy has been and continues to be used in clinical studies involving a number of additional symptoms that arise from an imbalance in neurochemicals. The symptoms include those in patients with Parkinson’s disease, chronic osteoarthritis pain, and post surgical pain. Although the numbers of therapy sessions differ, the Nexalin electrical stimulation has consistently shown positive results and statistically significant results in most cases. Furthermore, the improvements are clinically significant and lasting, typically for months, with no statistically significant drop off. We believe that this provides strong support for Nexalin Therapy’s positive and durable effects on the hypothalamus and associated brain structures.

Attachment A is included to provide more detailed information on the function of key brain structures.

---

1 U.S. Patent #6904322B2
Brain Stimulation using Nexalin Technology:
A Non-Invasive Method of Treating Anxiety, Depression and Insomnia
HOW DOES NEXALIN ADVANCED THERAPY WORK?

As stated earlier, the brain is the most complex organ of the human body, thus the exact mechanism by which Nexalin Advanced Therapy produces such dramatic results is not fully understood. However, data suggest that the patented waveform delivered during the Nexalin Therapy effects the hypothalamus and associated brain structures. A key indicator of this effect is a significant change in levels of enkephalins and beta-endorphins in the cerebral spinal fluid and brain structures, as well as other neurochemicals including serotonin and substance P.

A major function of the hypothalamus is to maintain homeostasis by constantly sensing and adapting to information received by the brain. When the body is faced with a degenerative or chronic process the hypothalamus appears unable to maintain normal levels of serotonin, beta-endorphins and other neuropeptides, neurotransmitters and neuromodulators. The result of reduced levels of these important neurochemicals can be anxiety, depression, and insomnia; which can increase in frequency and severity if not treated.

Nexalin Therapy consists of consecutive, daily treatment sessions. Through this repetitive stimulation of the hypothalamus, Nexalin Therapy can trigger significant changes in the levels of important neurochemicals within the brain. Since the hypothalami's primary job is maintaining the body in a stable, constant condition (homeostasis), changes in the normalized levels of neurochemicals including serotonin, beta-endorphins, and substance P may then be used within the brain to effect a response, i.e., “stop the degenerative or chronic process” – to restore, rebalance, and renew the homeostasis. We believe that Nexalin Therapy assists the hypothalamus to re-establish and sustain these neurochemicals at the brain’s healthy, normalized levels, resulting in prolonged improvement, as observed in recent clinical studies.

SCIENTIFIC EVIDENCE

Nexalin’s Patented Waveform

The Nexalin device produces a patented waveform that provides transcranial electrical stimulation (TES) delivered at a frequency of 77.5 Hz. This unique frequency results in the greatest increase in beta-endorphins as illustrated in Figures 1 and 2. The study resulted in an average of 580% increase (p<0.001) in beta-endorphins in the cerebral spinal fluid measured in patients with chronic spinal pain and 350% increase (p<0.001) in normal patients with no chronic pain symptoms.

2 U.S. Patent #6904322B2
3 CHANGE IN THE BETA-ENDORPHIN LEVELS IN BRAIN AND CEREBROSPINAL FLUID IN TRANSCRANIAL ELECTROANALGESIA, L. N. Airapetov, A. M. Zaitchik, M. S. Trukmanov, V. P. Lebedev, V. A. Sorokoumov, Ya.S. Katsnelson, V. G. Abisogomian, and Yu. K. Kodzaev, Pavlov Institute of Physiology of the USSR Academy of Sciences, Pediatric Medical Institute, Leningrad, USSR
5 CHANGE IN THE BETA-ENDORPHIN LEVELS IN BRAIN AND CEREBROSPINAL FLUID IN TRANSCRANIAL ELECTROANALGESIA, L. N. Airapetov, A. M. Zaitchik, M. S. Trukmanov, V. P. Lebedev, V. A. Sorokoumov, Ya.S. Katsnelson, V. G. Abisogomian, and Yu. K. Kodzaev, Pavlov Institute of Physiology of the USSR Academy of Sciences, Pediatric Medical Institute, Leningrad, USSR
Figure 1 – Amount of Beta-Endorphin in the Cerebral Spinal Fluid (CSF) in Chronic Spine pain patients when stimulated using TES at 77 Hz. In patients with chronic pain, beta-endorphin concentration was 1.5-times lower than that in normal subjects and had average value of 11.9±0.8-pmole/l. After 30-min. electrostimulation, average CSF beta-endorphin concentrations to increase 580% to reach the level of 69.9±7.5-pmole/l (p < 0.001).

Figure 2 – Amount of Beta-Endorphin in the Cerebral Spinal Fluid (CSF) in normal patients when stimulated using TES at 77 Hz. Average beta-endorphin concentration in CSF of normal individuals was 19.1±0.9-pmole/l. Transcranial electro analgesia caused average beta-endorphin concentrations to increase 350% (p < 0.001) and to reach the level of 67.6±7.6-pmole/l. 15 minutes after the end of electrostimulation, no significant increase in the beta-endorphin levels were observed (p < 0.05).
THE CLINICAL RESULTS

The results of a double-blind-placebo controlled Phase II Study, Using Nexalin Advanced Therapy to Treat Symptoms Associated with Mild to Moderate Depression Episodes, showed a statistically significant reduction in symptoms for those patients treated with “active Nexalin devices + placebo drugs” (Figures 3 and 4). These results indicate that Nexalin Therapy continues to show improvement during the 12 weeks after therapy. Patients treated with Nexalin Therapy reported normal behavioral responses (measured using the Hamilton Depression Rating Scale (HAM-D\textsuperscript{21}) and the Hamilton Anxiety Rating Scale (HAM-A\textsuperscript{21})) that lasted the entire 12-week follow up period\textsuperscript{6}.

---

\textsuperscript{6} Phase II Study, Using Nexalin Advanced Therapy to Treat Symptoms Associated with Mild to Moderate Depression Episodes.
In addition to the Hamilton scales, the clinical study also used the BDI (Beck) Scale, the MADRS, the HADS$_D$, and HADS$_A$ Scales. The different methods produced results that correlated in all cases as can be seen in the Table 1 below.

### Table 1 - Correlations of Different Scales - all depression and anxiety scales had high and very significant bivariate correlations with the Correlation Coefficient > 0.75

<table>
<thead>
<tr>
<th>Control Variable – treatment day</th>
<th>HAM_D</th>
<th>HAM_A</th>
<th>MADRS</th>
<th>BDI</th>
<th>HADS_A</th>
<th>HADS_D</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>825</td>
<td>825</td>
<td>825</td>
<td>825</td>
<td>825</td>
<td>825</td>
</tr>
<tr>
<td><strong>Correlation</strong></td>
<td>1.000</td>
<td>.942</td>
<td>.925</td>
<td>.855</td>
<td>.789</td>
<td>.798</td>
</tr>
<tr>
<td>Sig (2-tailed)</td>
<td>.</td>
<td>.0001</td>
<td>.0001</td>
<td>.0001</td>
<td>.0001</td>
<td>.0001</td>
</tr>
<tr>
<td><strong>HAM_A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Correlation</strong></td>
<td>.942</td>
<td>1.000</td>
<td>.929</td>
<td>.849</td>
<td>.808</td>
<td>.783</td>
</tr>
<tr>
<td>Sig (2-tailed)</td>
<td>.0001</td>
<td>.</td>
<td>.0001</td>
<td>.0001</td>
<td>.0001</td>
<td>.0001</td>
</tr>
<tr>
<td><strong>MADRS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Correlation</strong></td>
<td>.925</td>
<td>.929</td>
<td>1.000</td>
<td>.846</td>
<td>.740</td>
<td>.809</td>
</tr>
<tr>
<td>Sig (2-tailed)</td>
<td>.0001</td>
<td>.0001</td>
<td>.</td>
<td>.0001</td>
<td>.0001</td>
<td>.0001</td>
</tr>
<tr>
<td><strong>BDI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Correlation</strong></td>
<td>.855</td>
<td>.849</td>
<td>.846</td>
<td>1.000</td>
<td>.824</td>
<td>.904</td>
</tr>
<tr>
<td>Sig (2-tailed)</td>
<td>.0001</td>
<td>.0001</td>
<td>.0001</td>
<td>.</td>
<td>.0001</td>
<td>.0001</td>
</tr>
<tr>
<td><strong>HADS_A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Correlation</strong></td>
<td>.789</td>
<td>.808</td>
<td>.740</td>
<td>.824</td>
<td>1.000</td>
<td>.772</td>
</tr>
<tr>
<td>Sig (2-tailed)</td>
<td>.0001</td>
<td>.0001</td>
<td>.0001</td>
<td>.0001</td>
<td>.</td>
<td>.0001</td>
</tr>
<tr>
<td><strong>HADS_D</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Correlation</strong></td>
<td>.798</td>
<td>.783</td>
<td>.809</td>
<td>.904</td>
<td>.772</td>
<td>1.000</td>
</tr>
<tr>
<td>Sig (2-tailed)</td>
<td>.0001</td>
<td>.0001</td>
<td>.0001</td>
<td>.0001</td>
<td>.0001</td>
<td>.</td>
</tr>
</tbody>
</table>

In addition to the Hamilton scales, the clinical study also used the BDI (Beck) Scale, the MADRS, the HADS$_D$, and HADS$_A$ Scales. The different methods produced results that correlated in all cases as can be seen in the Table 1 below.

### DEMONSTRATED CLINICAL SAFETY

The Nexalin device has undergone extensive safety analysis with the results clearly indicating that the device is safe for its intended use. Additionally, the classification of the device places it into a non-significant risk (low risk device) category.

A review of Phase III Pivotal Clinical Trials (with a follow up period of one year) demonstrates that Nexalin Therapy does not result in any significant untoward responses. In fact, there was no significant difference between reported events in the placebo group and reported events in the active treatment group (Figure 5)
HOW IS THE THERAPY ADMINISTERED?

The patented waveform of Nexalin Advanced Therapy is administered through medical grade conductive pads that are produced specifically for the Nexalin technology. The pads are placed on the forehead and behind each ear, and are connected to the Nexalin device with thin cables.

Nexalin Advanced Therapy is a highly effective, yet soothing treatment. Most patients feel nothing during Nexalin Therapy. At Nexalin Advanced Therapy Centers, patients are treated to a quiet, 45-minute session where many actually relax to the point of sleep during a session. Relief starts as early as the first therapy and most by the third.

CONCLUSION

The brain is the most complex and least understood organ of the human body. Nexalin Therapy appears to provide stimulation that affects the hypothalamus and associated brain structures to adapt and alter the levels of neuropeptides, neurotransmitters and neuromodulators critical to maintaining normal mood behavior. This effect is long lasting. It is hypothesized that with a maintenance program normalization can be maintained for prolonged periods.

The other important factor is that at the completion of the Nexalin Therapy the hypothalamus has either adapted to a new level and stabilized or is in the process of stabilizing, resulting in the long lasting benefit.
REFERENCES:

1. Excerpts from a special report by Helen Philips, NewScientist.com news service, 04 September 2006

2. CHANGE IN THE BETA-ENDORPHIN LEVELS IN BRAIN AND CEREBROSPINAL FLUID IN TRANSCRANIAL ELECTROANALGESIA


4. Robust and tissue-specific expression of TPH2 versus TPH1 in rat raphe and pineal gland
   Paresh D. Patel, Crystal Pontrello and Sharon Burke

5. Brain Basics: Know Your Brain, National Institute of Neurological Disorders and Stroke (part of the National Institutes of Health), NIH Publication No.01-3440a, last updated May 01, 2007

6. Neuroscience Tutorial, created by Diana Weedman Molavi, PhD at the Washington University School of Medicine; Washington University Program in Neuroscience, copyright 1997


8. Excerpts from KidsHealth website, created by The Nemours Foundation's Center for Children's Health Media; updated and reviewed by: Steven Dowshen, MD; July 2007
ATTACHMENT A
FUNCTION OF KEY BRAIN STRUCTURES

An overview of the endocrine system, and more specifically the hypothalamus, is provided below to help you better understand the impact of Nexalin® Advanced Therapy’s stimulation on these vital areas of the brain.

The Hypothalamus

Within the body’s endocrine system, the hypothalamus a collection of specialized cells located in the lower central part of the brain. This vital area is the control center of all autonomic regulatory activities of the body. It has been said that the hypothalamus is the “brain of the brain.” It is also:

- An important emotional center, controlling the molecules that make you feel exhilarated, angry, or unhappy.\(^7\)
- The hub for automatic (or subconscious) and endocrine homeostatic systems such as cardiovascular, temperature, and abdominal visceral regulation.
- Management system for all endocrine hormonal levels, sensory processing, and organizing body metabolism, as well as ingestive behaviors.

The hypothalamus is the primary link between the endocrine and nervous systems; it appears that almost everything the hypothalamus does is related in some way to the management of the brain and body connection. Nerve cells in the hypothalamus control the pituitary gland by producing chemicals that either stimulate or suppress hormone secretions from the pituitary.

The hypothalamus is responsible for maintaining homeostasis, the body’s regulation of its internal environment so as to maintain a stable, constant condition. To maintain homeostasis, the hypothalamus is constantly adapting to stimuli from the five senses (sight, hearing, touch, taste, smell) as well as feedback from the nervous and endocrine systems.

“Once the hypothalamus is aware of a problem, how does it fix it? Essentially, there are two main outputs: neural signals to the autonomic system and endocrine signals to/through the pituitary.”\(^8\)

The hypothalamus controls pituitary output by secreting specific chemicals to the pituitary’s front lobe. If the hypothalamus is the “command center,” the pituitary gland is the “first lieutenant.” “The pituitary gland is often portrayed as the ‘master gland’ of the body. Such praise is justified

---

\(^7\) Brain Basics: Know Your Brain, National Institute of Neurological Disorders and Stroke (part of the National Institutes of Health), NIH Publication No.01-3440a, last updated May 01, 2007

\(^8\) Neuroscience Tutorial, created by Diana Weedman Molavi, PhD at the Washington University School of Medicine; Washington University Program in Neuroscience, copyright 1997
in the sense that the anterior and posterior pituitary secretes a battery of hormones that collectively influence all cells and affect virtually all physiologic processes. *The pituitary gland may be king, but the power behind the throne is clearly the hypothalamus.*

The paraventricular nucleus (PVN) is an aggregation of neurons in the hypothalamus, which produces many hormones. It is adjacent to the third ventricle (hence the name of the nucleus.) Although it is in the periventricular zone, it is not to be confused with the periventricular nucleus that occupies a more medial, subjacent position to the third ventricle. The PVN is highly vascularised and is within the blood-brain barrier, although the neuroendocrine neurons in this nucleus project to sites (the median eminence and the posterior pituitary) that lack a blood-brain barrier.

**Neurochemicals**

The brain produces more than 50 identified active drugs. Some of these are associated with memory, others with intelligence, still others are sedatives. Some of the neurochemicals believed to be affected by Nexalin Therapy are:

- **Endorphin** – Called the brain's painkiller, it is 3 times more potent than morphine.
- **Serotonin** – An opiate-like chemical that helps maintain a "happy feeling," and seems to help keep our moods under control.
- **Melatonin** – Produced by the pineal gland, regulates behavioral and physiological circadian rhythms. Levels of melatonin in the blood are highest prior to bedtime.
- **Dopamine** – Similar to adrenaline; it affects brain processes that control movement, emotional response, and ability to experience pleasure and pain. The brains of people with Parkinson's disease contain almost no dopamine.
- **Substance P** – In the central nervous system, is associated with the regulation of mood disorders, anxiety, stress, reinforcement, neurogenesis, neurotoxicity and pain.
- **Acetylcholine** – The first neurotransmitter ever identified, it is particularly important in the stimulation of muscle tissue. In high doses, it can cause convulsions and tremors. In deficient levels, it can contribute to motor dysfunction.

Neurologists have long been aware of four classical neurotransmitters: epinephrine, norepinephrine, serotonin, and acetylcholine, but recently there have emerged a large number of additional neurotransmitters, of which an important group is the *neuropeptides*. While neuropeptides function as neurotransmitters, some of them also perform the role of *neuromodulators*; they do not act directly as neurotransmitters but rather as inhibitors or stimulators of neurotransmission. Opiates are a group of neuropeptides that act as both neurotransmitters and neuromodulators. Opiates’ are so named because they are the naturally occurring neuropeptides with a strong affinity to the receptors that bind opiate drugs such as morphine and heroin. In effect, they are the body's opiates.

---


10 Paraventricular nucleus of hypothalamus - Wikipedia

Brain Stimulation using Nexalin Technology;
A Non-Invasive Method of Treating Anxiety, Depression and Insomnia
The Endocrine System

“Although we rarely think about them, the glands of the endocrine system and the hormones they release influence almost every cell, organ, and function of our bodies. The endocrine system is instrumental in regulating mood, growth and development, tissue function, and metabolism, as well as sexual function and reproductive processes. Even though the nervous system and endocrine system are separate systems, they often work together to help the body function properly.

The foundations of the endocrine system are the hormones and glands. As the body’s chemical messengers, hormones transfer information and instructions from one set of cells to another. Hormone levels can be influenced by factors such as stress, infection, and changes in the balance of fluid and minerals in blood.

A gland is a group of cells that produces and secretes, or gives off, chemicals. Some types of glands release their secretions in specific areas. Endocrine glands release more than 20 major hormones directly into the bloodstream where they can be transported to cells in other parts of the body.

The major glands that make up the human endocrine system are the hypothalamus, pituitary, thyroid, parathyroids, adrenals, pineal body, and the reproductive glands.

The Pituitary Gland

The pituitary gland is located at the base of the brain just beneath the hypothalamus and is considered the most important part of the endocrine system. It's often called the "master gland" because it receives instructions from the hypothalamus and then releases hormones that control the thyroid and adrenal glands. The production and secretion of pituitary hormones can be influenced by factors such as emotions and seasonal changes. To accomplish this, the hypothalamus relays information sensed by the brain (such as environmental temperature, light exposure patterns, and feelings) to the pituitary. One of the hormones secreted by the pituitary is endorphins, chemicals that act on the nervous system to reduce sensitivity to pain.”

The Pineal Gland

The pineal body, also called the pineal gland. The pineal gland is a small organ shaped like a pine cone (hence its name) located in the middle of the brain. The pineal gland synthesizes and secretes melatonin, a structurally simple hormone that communicates information about
environmental lighting to various parts of the body. The duration of melatonin secretion each day is directly proportional to the length of the night. The light-transducing ability of the pineal gland has led some to call the pineal the "third eye". The secretory activity of the pineal gland has been shown to be influenced by environmental light conditions. The duration of melatonin secretion each day is directly proportional to the length of the night.

The light-transducing ability of the pineal gland has led some to call the pineal the "third eye".

**The Limbic System**

The **limbic system** wraps around the brain stem and is beneath the cerebral cortex. It is a major center for emotion formation, behavior, learning, and memory. The limbic structures are also connected with other major structures such as the cortex, hypothalamus, thalamus, and basal ganglia.

The structures of the limbic system are highly interconnected with the rest of the brain, and they likely form a gateway for communication between the cerebral cortex and the hypothalamus. This gateway allows for cognitive processes to modify the affect of the limbic system on hypothalamic functions, which provides a more extensive adaptive mechanism in an effort to normalize.

**Figure A-3**
A Highly Effective Treatment for Anxiety, Depression, and Insomnia without Serious Side Effects

Nancy E. White PhD, LPC, LMFT, AAC
Unique Mind Care, Houston, TX  77056

ABSTRACT

The number of people in this country exhibiting symptoms of depression and anxiety continues to grow and is projected to continue growing through the next decade at least. The symptoms of these disorders cause substantial distress for the sufferers and their families and cost society dearly each year in lost time and suboptimal job performance. Recent research has raised questions about the effectiveness of medications long considered a standard of care in the treatment of these conditions. In light of this information it seems appropriate to explore alternative therapies that demonstrate a high level of effectiveness in mediating anxiety and depression without serious side effects.

This presentation reviews and evaluates the outcomes of a clinical study involving anxious and/or depressed patients who were treated in a clinical setting using a specific form of transcranial electrical stimulation (TES) that lightly stimulates the hypothalamus and associated brain structures at a frequency shown to encourage the normalization of neurochemistry. The purpose of the present study has been to replicate the effectiveness of this TES protocol in the everyday clinical setting using as measurement standards the quantitative EEG (QEEG) and a multifaceted battery of pre- and post-tests and scans readily available in the clinical setting.

The value of targeting the hypothalamus is discussed, rationalizing that approach as a key to highly effective outcomes. Then, the treatment outcomes of a population undergoing TES in the clinical setting are summarized and several case studies presented to illustrate more specifically the potential of TES as a therapeutic treatment and what may be its implications for treating the symptoms of aging.

Keywords: TES, transcranial electrical stimulation, depression, bipolar, anxiety, hypothalamus, neurochemistry.

INTRODUCTION

In an average year in the U.S. some 40 million people suffer from anxiety and another 20 million become clinically depressed. The symptoms of these disorders cause substantial distress for the sufferers and their families and cost society dearly each year in lost time and suboptimal job performance. Moreover, the number of people exhibiting symptoms of depression and anxiety continues to grow and is projected to continue growing through 2020. Persons who cannot find an effective solution to their depression or anxiety tend to get worse and develop dysfunctional behaviors and habits as they seek to compensate, making treatment even more complex. These behaviors and habits not only complicate treatment, but can speed the progress of degenerative diseases and advance the aging process.

Medication has been considered a primary course of treatment for mood disorders in conventional medicine and its use continues to increase. For instance, the number of Americans taking antidepressants alone has doubled in the last decade. Now recent research has raised questions about their actual effectiveness.

A recently published study submitted to the FDA examined the current status of research on antidepressant drugs’ effectiveness. The study, involving four meta-analyses of antidepressant efficacy, suggested that antidepressants may be only marginally efficacious compared with placebos. Further, the authors document profound publication bias that apparently inflates efficacy figures. Considering this information in light of the drugs’ side effects – including death via suicide or uncontrolled behavior – it may make sense to explore therapies shown to be highly effective for anxiety and depression without serious side effects.

One such path leads to forms of brain electrical stimulation amenable to administration in the office setting. The first experiments with low intensity electrical stimulation of the brain were conducted by Drs. Leduc and Roux in 1902. As the field has progressed several technologically advanced methods of brain electrical stimulation have found their way into current practice: Transcranial electrical stimulation...
(TES) – European and U.S. methods, cranial electrical stimulation (CES), and transcranial magnetic stimulation (TMS). Table 1 outlines the characteristics, treatment focus, applications, contraindications and reported effectiveness levels of each.

**Table 1. Technology Evaluation**

<table>
<thead>
<tr>
<th>Type of Brain Stimulation</th>
<th>Treatment Protocol/Duration</th>
<th>Treatment Focus</th>
<th>Applications</th>
<th>Contraindications</th>
<th>Effectiveness</th>
<th>Duration and Cost of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>TES (Transcranial Electrical Stimulation)</td>
<td>Rectangular Pulse of 1.0-5.0 mA administered via pads on forehead and each mastoid, 5-20 sessions lasting 30-45 min., depending on condition</td>
<td>Psycho-physiological effects of stimulating endorphinergic and antiocceptive structures (medial brainstem)</td>
<td>Stress, Depression; alcohol/drug withdrawal; pain syndromes, migraine; hypertension; speeding up wound healing; immune stimulation; endometriosis; sports injuries</td>
<td>Seizures, Epilepsy; acute brain injury/infection, brain tumors; Hydrocephaly; hypertensive crisis; acute psychiatric disorders, implanted electronic stimulators; under 5 y</td>
<td>20-30% acceleration of wound healing; 81% long term remission in gastric ulcers/pain. Persistence varies</td>
<td>Not approved by FDA</td>
</tr>
<tr>
<td>TES - U.S. Method (Device approved by FDA)</td>
<td>Rectangular AC pulse administered via pads on forehead and each mastoid, 10-15 treatments of 40 min. duration in groups of five consecutive sessions. Additional sessions if indicated.</td>
<td>Psycho-physiological effects of balancing neurochemistry through benzodiazepine stimulation of the hypothalamus</td>
<td>Treatment of Depression, Anxiety and insomnia. Studies underway for Parkinson's, Osteoarthritis; other studies in prospect</td>
<td>Seizures, Epilepsy; acute brain injury/infection, brain tumors; Hydrocephaly; hypertensive crisis; acute psychiatric disorders, implanted electronic stimulators; under 13 y</td>
<td>Avg Improvement after 2-3 wks: Anxiety = 77%; Depression = 74%; Insomnia = 84%. Persistence = &gt;1 yr.</td>
<td>Two to three weeks $4,500 - $6,750</td>
</tr>
<tr>
<td>CES (Cranial Electrical Stimulation)</td>
<td>Bipolar asymmetrical Rectangular wave 10-600 mA, adjustable. Administered via earlobe electrode on each earlobe @ mastoid. Used in office or at home 20-40 min. daily or as needed.</td>
<td>Moves to normalize electrical activity of the brain and nervous system</td>
<td>Stress reduction; improvement of anxiety, depression and insomnia symptoms</td>
<td>Pregnancy, significant hypotension, implanted electronic stimulators. Use only @ mastoid.</td>
<td>Anxiety: 67% had improvement of 50%; Depression: avg. 50% reduction; weeks or more studies = significant pain reduction. Persistence low</td>
<td>Two to three weeks $400 up</td>
</tr>
<tr>
<td>TMS (Transcranial Magnetic Stimulation)</td>
<td>Focused pulsed magnetic field (electromagnetic induction) administered via magnetic coil (several types) placed next to the head, 15-30 treatments of 40 min. duration.</td>
<td>Stimulation of the areas of the brain thought to control mood</td>
<td>Treatment of depression, including severe depression. Research underway for tinnitus, Parkinson's, schizophrenia</td>
<td>History of seizures, epilepsy; cerebrovascular disease; implanted electrical stimulators; metal implants in or near head; efficacy not established &lt;2y or &gt; 70yo</td>
<td>(1) Avg improvement in depression after 4-6 wks = 22.1%; (2) Recovery rate after 3 wks = 14%. Persistence = 6 mo. +</td>
<td>Four to six weeks $8,000 - $12,000</td>
</tr>
</tbody>
</table>

**TRANSCRANIAL ELECTRICAL STIMULATION – US METHOD**

The U.S. method of TES was selected for use in programs of treatment for functional brain problems, mood disorders, and emotional trauma. The FDA approved device delivering this form of TES works to normalize neurochemistry by benignly stimulating the hypothalamus and associated brain structures using a specific, patented waveform and frequency. No serious side effects have been reported and it appears to provide a high level of positive outcomes.

The hypothalamus, often called “the brain’s brain” or “the seat of emotion”, attracts attention as an appropriate target for this TES approach to mediating mood disorders because of its wide role in maintaining homeostasis in the brain-body system, including the use of various neurotransmitters, distributed among its nuclei, in its control of the pituitary or which it releases into the bloodstream in the pituitary. Electrical stimulation studies reveal pleasure centers in the hypothalamus (ventral and lateral) as well as centers for anger and rage (anterior and dorsal), pain (central and posterior), and fear (dorsal and posterior). These and other centers in the hypothalamus release chemical messengers designed to mediate conditions pertaining to them. The U.S. method of TES is designed to actively direct the hypothalamus to rebalance neuropeptides, neurotransmitters, and neuromodulators that are critical to maintaining normal mood and behavior.

The hypothalamus also connects with the amygdala and higher parts of the cerebral cortex, including the orbitofrontal cortex, either by direct projections or through the thalamus, facilitating interaction between physical and mental processes, including those interactions affecting mental and emotional states.
In particular, the hypothalamic-pituitary-adrenal (HPA) axis assumes considerable importance in depression. Pariante notes that depression is characterized by an overactivity of the HPA axis that resembles the neuroendocrine response to stress and that these HPA axis abnormalities participate in the development of depressive symptoms. While the exact mechanism by which this occurs is unknown, an increasing number of researchers believe that stress-induced HPA axis activation directly causes depressive symptoms by interacting with the brain neurotransmitter systems regulating these behavioral changes. The influence of TES on hypothalamic control of the HPA axis, by quieting the HPA circuit so to speak, may account for many of the positive neurobehavioral and physiological effects arising from this treatment.

**Clinical Methods Used to Treat and Monitor Patient Progress**

1. Quantitative EEG\(^{13}\) – A quantitative EEG (eyes closed) was performed both before and after the ten or fifteen sessions of TES. Quantitative EEG (QEEG or Brain Mapping) is the measurement, using digital technology, of electrical patterns at the surface of the scalp which primarily reflect cortical electrical activity or “brainwaves.” The QEEG is the analysis of the digitized EEG and involves comparison of the electrical activity generated from the patient's brain with a database of normal individuals. The QEEG is interpreted and used as a clinical tool to evaluate brain function and to track changes in brain function due to the intervention of the TES therapy.

2. 3D body scan\(^{14}\) – As part of the pre-post measurement for the patients undergoing treatment, the EIS system, a bio-impedance medical device, was chosen. This device measures the effect of the DC current in interstitial fluid of twenty two segments of the body. It is non-invasive, quick and low cost, and offers an understanding and measurement of the pre-conditions of the patient and the post-effect of the treatment with the TES. The body scan Wellness aspect of this device offered suggestions for good nutrition for each individual and this was deemed of value for the long-term support for the health and balance of the treated patient. The chiropractor indicators offered information as to the electrical flow of energy up the spine. A blockage could indicate that the brain was not receiving the energetic information for good function and perhaps not getting the full effect of the TES treatment. If an electrical block was seen a referral to a chiropractor for adjustments was indicated. Most importantly, for the purpose of this treatment, the brain analysis aspect of the EIS system allowed the monitoring of cerebral dopamine, cerebral serotonin, cerebral adrenalin and noradrenaline, and estimated acetylcholine. Neuronal excitability was monitored along with the tissue oxygen pressure and conductivity of the right and left frontal lobe and right and left limbic system.

3. A “0-10” scale for rating patient’s conditions on a daily basis pre- and post-treatment are used; “0” representing “symptom free” and “10” representing “very severe”. For consistency these same scales are used to rate anxiety, depression, and insomnia.

4. A clinical assessment of the patient’s condition is made by both therapist and doctor as the patient progresses through the treatment.

5. Additional testing is added based on the environmental history and factors experienced by the patient to prevent outlining factors from affecting the long-term effectiveness of our work. These tests include food sensitivity, micronutrients, metal toxicity, and neurotransmitter balance.

**Therapy**

The estimated time for the therapy session will be approximately 60 to 75 minutes per session. The patient will be seated comfortably in a reclining chair as most patients sleep through the treatment period. The forehead and mastoid areas (behind the ears) will be wiped down to remove oils and dirt that may be present in preparation for the application of the electrodes. Specifically designed single use electrode pads are then placed at each of these locations. To prevent miss connections a small cable with one snap and two connecting clips is used to connect the three pads to the TES Device. The device is then switched on to begin the treatment. Upon completion of the therapy the technician removes and discards the pads, interviews the patient, and escorts them out. On a selective basis, the medical director may also spend additional time with the patient. Patient follow-up may be for up to a year.
*Measured Results*

Traditional treatment might result in 25% of patients having >30% improvement. TES therapy has resulted in ninety percent (90%) of patients treated having > 50% improvement in their diagnosed condition, with the average improvement just under 80%. This coincides with the clinically observed improvements in the patients.

*Case Study #1*

Case study #1 is a high-functioning 50-year-old medical doctor who wanted to experience the TES therapy before she began referring patients. Prior to therapy she was described as distractible. After 10 sessions of the TES therapy her dominant brain wave frequencies (Hz) increased significantly, which is generally considered desirable for an awake, alert, and high-functioning adult (See Figure 1). Moreover, her brain wave amplitudes (power) moved toward a more optimal balance; slow wave power decreased significantly (36%-51%; \[p< 0.000\]) while the power of the frequency bands supporting concentration and on-task behavior (“alpha,” particularly high-alpha, and “beta,” particularly low-beta) increased significantly (78%-87%; \[p<0.000\]), (See Figure 2).

She is now even more functional and more highly productive than before, evidenced not only by her writing four training manuals in a short period without effort, but by significant strides she has made – and is making – to enhance her medical practice. She reports being more organized and functional. She feels great and thinks the planet could benefit from having everyone do this treatment.

![Figure 1. Case 1: QEEG, before and after TES treatment.](image-url)
**Case Study #2**

TP had been a typical healthy and functional 17-year-old male, well-liked by most who knew him. He had a recreational marijuana habit and had been offered some “pot” which apparently had been laced with a powerful foreign narcotic. Within 36 hours he was in complete psychosis. He spent two weeks locked up in the psychiatric department of a major hospital from which he emerged no better. He then spent four weeks in the psychiatric unit of another major hospital where he was diagnosed as bipolar and given a list of medications that his father said made him a “zombie.” He was sent to a third hospital where doctors told his father and his grandparents that they could do no more for him and that he would have to be cared for the rest of his life. He was then sent home with four medications.

Of necessity, he had dropped out of school during his senior year when his psychosis began and was subsequently unable to return to classes. Once home, this previously popular teenager became a recluse with extreme social anxiety and psychotic episodes (hearing voices, etc.). At one point he was found walking down the street in the middle of the night. He didn’t know his name or where he was.

At the suggestion of his best friend’s mother, who had begun investigating treatments that could be helpful to him, his father and grandparents called the Enhancement Institute to investigate the possibility that TES could provide hope for the young man’s recovery. His family drove him 80 miles each way for extensive testing and evaluation, then later on for the three week period of five consecutive treatments each.

Initially he was severely depressed, highly anxious, and heavily affected by prescription drugs. He threw up prior to the first and second days’ treatments and barely spoke during the first week. After the first week it was like working with a completely different person than that who initially came for therapy. Our medical director was reducing his meds as fast as was safe. He had become friendlier, had gained near-normal affect and carried on effortless conversations with staff, but still reported extreme social anxiety. For instance, he refused to go into public places, such as a restaurant; rather, he would sit in the car while his grandparents got food to take with them. By the last day of his treatment he was willing to go into a restaurant to eat. There was no further socially anxious behavior a month after the therapy ended and a six month follow-up confirmed that there have been no repeat episodes of psychotic behavior or hearing voices.

A remarkable feature of the young man’s post-treatment QEEG compared with his pre-treatment readings was the reduction in left frontal alpha (8-9 Hz)(Figure 3). A pattern of left frontal hypoactivation,
particularly in the alpha range, is a pattern found by Davidson’s research to be indicative of possible depression.\textsuperscript{15} Measured improvements ranged from 54\% - 67\% [p<0.000] (Figure 4).

Figure 3. Case 2: QEEG, before and after TES treatment.

Figure 5 illustrates differences in the pre- and post-analysis of the 3D body scan. Right and left frontal lobe conductivity, right and left frontal lobe tissue oxygen pressure, neuronal excitability, estimated cerebral serotonin, estimated cerebral dopamine, estimated cerebral adrenaline/noradrenaline and estimated acetylcholine are measured. Initially there is a predominance of out-of-range readings. After 15 sessions of the TES all the identical readings are in range except left frontal tissue oxygen pressure and
estimated acetylcholine. Actually, left frontal tissue oxygen pressure is barely low, with a measurement score of 43 – the norm being 44 to 46, leaving only estimated acetylcholine clearly out of range with a measurement of 50 versus a normal range of 22-34 (Figure 5).

Figure 6 offers a graphic of estimated cerebral serotonin, estimated cerebral adrenaline/noradrenaline and estimated cerebral dopamine. The green bar represents normal range. The first measurements were well out of range, while all three neurochemicals normalized post-treatment, measuring in the center of the normal range.

His family is thrilled to have their son and grandson back and functioning normally. In the five month follow-up, he has had no more episodes of psychosis and is quite normal with no medication and has overcome his social anxiety. He took his GED and passed it and has now entered college successfully.
**Case Study #3**

Case Study #3 involves a 19 year-old college student diagnosed with depression, traumatic brain injury (TBI), and bipolar disorder. He had been referred based on a prior evaluation using the 3D body scan. He arrived with his mother with whom he was quite angry. He wouldn’t look at anyone and exhibited an inability to talk. Although he had been a jogger in the past his body was so out of balance that he was unable to run at the time he came for therapy. He was hearing voices and exhibiting bipolar tendencies, evidenced by the first three data points on the charts in Figures 10 and 11 and the “before” chart in Figure 7.

![Figure 7. Case: 3D body scan, before and after 3 TES treatments.](image)

His pre-treatment scan and those taken during the first week of treatment showed unstable neurochemistry, conductivity, and neuronal excitability, suggesting a basis for his bipolar disorder (in Figures 10 and 11 the green band represents normal range). This instability continues through the first week of treatment even though the neurochemistry was beginning to normalize as evidenced by charts in Figures 7 and 8. Beginning with the second week of treatment his measurements of neuronal excitability moved to the center of normal range as measured in Figure 8. Estimated cerebral serotonin, dopamine, and adrenaline/noradrenaline, which exhibited pretreatment instability similar to that of neuronal excitability, showed similar improvement at the beginning of the second week. The conductivity measure in Figure 11 also showed initial instability, visible in the right frontal lobe, left frontal lobe and the left limbic region, and these began to normalize in the second week of treatment. The right limbic system remained normal pre and post-treatment. The normality seen in the measures at the beginning of the second week persisted through the remainder of treatment and 3 months of follow-up as evidenced in Figure 9. Although not contained in the measures shown, normal measures had maintained in a five month follow-up.

After the end of the first week the patient became more communicative and his activities were returning to normal. He returned to jogging in the mornings, as had been his pre-illness routine, even though he was in a strange city. No further bipolar behavior was observed and this has been consistent through the five months of follow-up.

In his post treatment interview, the patient reported that when he first arrived he was unable to find words, which created his inability to talk. He reported that during the first few days of treatment he had been unable to think of words. He then progressed to finding the words but was unable to form them or speak them. Toward the end of the first week he began speaking fluently and then told us that he could now find words, form words, and then speak the words. His depression was also resolved and upon returning home he began living a more normal life and was better able to interact with his friends.
Figure 8. Case 3: 3D body scan, after the 6th and 10th TES treatment.

Figure 9. Case 3: 3D body scan, three month follow-up after the end of the TES treatment.
Figure 10. Case 3: 3D body scan, 4 month chart of progress viewing changes in neuronal excitability.

Figure 11. Case 3: 3D body scan, 4 month chart of progress viewing changes in neurochemistry and brain conductivity.
CONCLUSIONS

Results from the review of clinical case studies show that the QEEGs and scans were effective tools for monitoring pre- and post-TES therapy, clearly showing the improvements achieved. The TES therapy was shown to be highly effective (>90% of cases), resulting in normalized brain neurochemistry and activity within two to three weeks. This was consistent with the original clinical results, in that the patients in these case studies achieved normal levels of behavior post therapy. Other therapies were used on a case-by-case basis to resolve additional patient issues identified by the scans.

REFERENCES


ABOUT THE AUTHOR

Nancy E. White, PhD, LPC, LMFT, AAC is a licensed Clinical Psychologist in the State of Texas as well as a Licensed Marriage and Family Therapist and Advanced Addiction Counselor. She is the Founder and Clinical Director of The Enhancement Institute, Houston, Texas, which focuses on neurobehavioral wellness. Dr. White has practiced in the field of Neurofeedback and Neuromodulation for more than twenty years and has trained many other practitioners in the use of these protocols. She is a Certified EEG Fellow of the Biofeedback Certification Institute of America (BCIA) and a Diplomat of the Quantitative EEG Certification Board.

Dr. White is a Fellow of the International Society for Neurofeedback and Research (ISNR) and served on its Board of Directors (2006-2009) as President-Elect (2006-07), President (2007-08), and as Past President (2008-09). Other leadership positions she has held in her field include:
- Member of the Association for Applied Psychophysiology and Biofeedback (AAPB) and member of the Board of Directors of its Neurofeedback Division (2006-2008).
- Member of the Quantitative EEG Certification Board (1995-present).
September 13, 2010

A brief history of Nexalin use in a psychotic patient taking a variety of medications.

The patient, MM, is a 32 year old single Caucasian male from out-of-state who came to California for drug rehabilitation and to be assessed and treated by me for any hormone or nutrient imbalance that may be causing some of his symptoms. MM has a long history of drug use, mostly cocaine or crack. He also has had a long psychiatric history, dating back to childhood, as an outpatient and at times as an inpatient. He has seen numerous psychiatrists and has been on a large variety of antipsychotic medications that included typical and atypical antipsychotics. The most recent one was Abilify that left the patient in a chronic state of discomfort that may contribute to drug cravings. The patient describes a history of early life trauma that includes numerous accounts of enduring physical violence. In addition, within the past year he lost his father and a year prior to that his younger brother who died in a fatal car crash. He states that though he has been diagnosed as either schizophrenic or Bipolar, his actual diagnosis is PTSD.

Although the patient was slowly weaned from his antipsychotic, Abilify, he had a rebound psychosis and felt unsafe. He stated he needed to be put away because he felt tremendous rage, in particular to another person at the rehab. He had an elaborate delusion concerning this person, yet still held out the possibility that he was delusional or psychotic. MM also suffered from depression and anxiety. He has had a long history of insomnia successfully treated with Seroquel, an atypical antipsychotic.

MM had suggested high doses of Seroquel in order to “bring him back to reality”. He was started on Seroquel XR 200 mg three times per day and Ativan 1 mg (a benzodiazepine) also three times per day in addition to his other medication, an antihypertensive for his high blood pressure, and Gabapentin, presumably for emotional lability. He was kept out of the hospital.

Instead he was sent to a residential detox facility for observation and where I was able to monitor him. The medications primarily had him sleeping most of the day for most days. Upon awakening he was still not very coherent and continued to describe the delusional material.

Nexalin had been planned even prior to his psychotic break. However I was hesitant to start Nexalin treatments under the circumstances. After talking with people familiar with Nexalin, I became comfortable with moving forward with Nexalin treatments.

It appeared to be the right thing to do in that the patient's response seemed almost miraculous. He had an immediate positive response after the first treatment, although he was still psychotic. His only complaint during Nexalin, so far has been a headache that he describes as bearable. As the patient continued Nexalin treatments, he’s had 2 weeks to date and is starting his third week. He is clear thinking and recognizes his prior thoughts as psychotic. He commented: “I was pretty crazy, wasn’t I?” His mood has improved and his level of anxiety for the most part is greatly diminished except for intermittent bouts triggered by distressing events. However, this has not lead to a return to his prior mental state.

There is a significant improvement in MM’s ability to socialize and he is relating to others more appropriately. His mood is significantly improved as evidenced by his ability to joke around with my staff prior to his appointment with me. In fact, most of us smile and shake our heads in amazement at MM’s “metamorphosis”. This is a very heartening result for this patient and look forward to his continued improvement.

Suzie Schuder, MD
Noninvasive Brain Stimulation with Low-Intensity Electrical Currents: Putative Mechanisms of Action for Direct and Alternating Current Stimulation

Soroush Zaghi, Mariana Acar, Brittney Hultgren, Paulo S. Boggio, and Felipe Fregni

Transcranial stimulation with weak direct current (DC) has been valuable in exploring the effect of cortical modulation on various neural networks. Less attention has been given, however, to cranial stimulation with low-intensity alternating current (AC). Reviewing and discussing these methods simultaneously with special attention to what is known about their mechanisms of action may provide new insights for the field of noninvasive brain stimulation. Direct current appears to modulate spontaneous neuronal activity in a polarity-dependent fashion with site-specific effects that are perpetuated throughout the brain via networks of interneuronal circuits, inducing significant effects on high-order cortical processes implicated in decision making, language, memory, sensory perception, and pain. AC stimulation has also been associated with a significant behavioral and clinical impact, but the mechanism of AC stimulation has been underinvestigated in comparison with DC stimulation. Even so, preliminary studies show that although AC stimulation has only modest effects on cortical excitability, it has been shown to induce synchronous changes in brain activity as measured by EEG activity. Thus, cranial AC stimulation may render its effects not by polarizing brain tissue, but rather via rhythmic stimulation that synchronizes and enhances the efficacy of endogenous neurophysiologic activity. Alternatively, secondary nonspecific central and peripheral effects may explain the clinical outcomes of DC or AC stimulation. Here the authors review what is known about DC and AC stimulation, and they discuss features that remain to be investigated.

Keywords: noninvasive brain stimulation; transcranial direct current stimulation; cranial electrotherapy; electrosleep; cranial AC stimulation; transcutaneous electrical stimulation; tDCS; tACS; CES; TCES; brain polarization

Beginning more than a century ago, neurophysiologists demonstrated great interest in learning about the effects of low-intensity (currents used usually equal to or less than 2 mA) electrical stimulation when applied to the human head. In this age of advanced technology, although relatively little is still known about the mechanism and effects of cranial electrical stimulation, these methods are becoming increasingly explored for their utility in investigating the effect of cortical modulation on various neural networks, and interest in the field remains strong.

Today we recognize two main forms of low-intensity cranial electrical stimulation: transcranial direct current stimulation (tDCS; a method in which low-intensity constant current is applied to the head) and cranial alternating current (AC) stimulation (in which low-intensity AC is applied to the head). tDCS offers a noninvasive method of brain stimulation and has been shown to be effective in modulating cortical excitability as well as guiding human perception and behavior (Nitsche 2008). In the past two years alone, numerous studies have been published on tDCS demonstrating positive clinical results. Although many groups have studied and reviewed the neurophysiologic and clinical effects of transcranial brain stimulation with direct current using modern techniques of brain research (Lefaucheur 2008; Nitsche 2008), less effort in recent years has been dedicated to the study of stimulation with nonconstant and alternating currents. Here we review and discuss the two main techniques of low-intensity cranial electrical stimulation (DC and AC stimulation), and we discuss potential mechanisms of action based on behavioral and neurophysiologic studies, providing new insights for the field of noninvasive brain stimulation.

From the Berenson-Allen Center for Noninvasive Brain Stimulation, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts (SZ, MA, BH, FF); and Cognitive Neuroscience Laboratory and Developmental Disorders Program, Center for Health and Biological Sciences, Mackenzie Presbyterian University, Sao Paulo, Brazil (PSB).

We acknowledge the Berenson-Allen Foundation and American Heart Association for partially funding this project.

Address correspondence to: Felipe Fregni, MD, PhD, Berenson-Allen Center for Noninvasive Brain Stimulation, 330 Brookline Ave, KS 452, Boston, MA 02215; e-mail: ffregni@bidmc.harvard.edu.
Methodology of Review

Medline and Scopus databases were searched for English-language articles published between 1980 and 2008, using the following keywords: transcranial direct current stimulation; tDCS; brain polarization; brain, electrical stimulation; brain, direct current; transcranial alternating current stimulation; cranial electrotherapy stimulation; transcutaneous electrical stimulation; brain, alternating current. Articles referenced within these sources were also selected if relevant to this review.

Historical Highlights

Applications of electrical stimulation of the brain, which include invasive and noninvasive modalities, are now burgeoning in the fields of the neurological sciences. On one end, techniques of deep brain stimulation allow for the focal and precise stimulation of deep neural structures (such as thalamic, subthalamic, and pallidal nuclei), which provide remarkable results in controlling undesirable tremors and dystonias, and are used clinically, for example, in the treatment of advanced Parkinson’s disease (Limousin and Martinez-Torres 2008). At the level of the cortex, electrodes left implanted at the epidural area above the motor cortex are used for motor cortex stimulation, a technique shown to alleviate many forms of chronic neuropathic pain (Lima and Fregni 2008). Although these methods of brain stimulation have shown marked progress, one limitation in their application is the requirement for the surgical penetration of the scalp, skull, and brain, a costly procedure that carries considerable risk. In this context, methods of noninvasive brain stimulation have regained significant appeal for their capacity to safely modulate brain activity.

Even so, the recent interest in low-intensity transcranial brain stimulation is not new. Low-intensity electrical stimulation probably had its origins in the research thrusts of the 18th century with studies of galvanic (i.e., direct) current in humans and animals by Giovanni Aldini and Alessandro Volta, among many others—based on the work of electrotherapy pioneers Johann Krüger (1715–1759) and Christian Kratzenstein (1723–1795) (Kaiser, 1977)—with a long and interesting history (see Goldensohn 1998; Priori 2003). As early as 1794, Aldini had assessed the effect of galvanic head current on himself (Aldini 1794), and by 1804, he had reported the successful treatment of patients suffering from melancholia (Aldini 1804). Research continued through the early 20th century; yet because DC induced variable results, or sometime none at all, the use of low-intensity DC (i.e., tDCS) was progressively abandoned in the 1930s when Lucino Bini and Ugo Cerletti at the University of Rome proposed the method of electroconvulsive therapy (ECT; Priori 2003), which involves transcranial stimulation at significantly higher intensities. Interesting and imaginative efforts revolving around ECT, particularly between 1938 and 1945, subsequently led to an interest in the application of AC at lower intensities with the first study of “cranial electrotherapy stimulation” (also known as “electrosleep”) published by Anan’ev and others in 1957 (Anan’Ev and others 1957). Limoge then identified a specific parameter of low-intensity AC stimulation in 1963 (“Limoge’s current”), which was noted to significantly reduce the amount of narcotics and neuroleptics required to maintain anesthesia when stimulation was applied during surgery (Limoge and others 1999). Since the 1960s, a series of studies with low-intensity AC stimulation have been published (Kirsch and Smith 2004; Smith 2007), and cranial AC stimulation devices have become commercially available for personal use (e.g., Alpha-Stim, Fisher Wallace Cranial Stimulator, Transair Stimulator, etc.). However, research in this area has been inconsistent and there remains a lack of solid evidence showing the effects of weak transcranial stimulation with AC.

At the turn of the millennium, interest in a new form of noninvasive brain stimulation, namely transcranial magnetic stimulation (TMS), renewed interest in other forms of noninvasive brain stimulation. Using TMS evoked motor potentials as a marker of motor cortex excitability, Nitsche and Paulus demonstrated the possibility of modulating cortical excitability with tDCS: Weak DC applied to the scalp was associated with excitability changes of up to 40% that lasted several minutes to hours after the end of stimulation (Nitsche and Paulus 2000). In fact, a mathematical model has shown that stimulation with DC could modify the transmembrane neuronal potential (Miranda and others 2006; Wagner and others 2007) and, in turn, influence the excitability of individual neurons without, however, actually eliciting an action potential.

Although recent evidence has been encouraging, the two main challenges for noninvasive methods of brain stimulation with weak currents are the limitations in focality and low intensity (i.e., subthreshold stimulation). In tDCS, the effect of weak currents delivered to the brain may be compensated for by the cumulative time-dependent effects of unidirectional polarizing stimulation (Nitsche and Paulus 2001; Paulus 2003). However, the mechanism of AC remains less understood because the direction of current is constantly changing and so the possibility of polarization with a weak current becomes unlikely. This raises a critical issue as to whether stimulation with weak AC can actually induce significant transcranial CNS effects or whether the clinical effects observed with AC stimulation are manifested through an alternative mechanism of action.
Noninvasive Brain Stimulation with Low-Intensity Direct Current (tDCS)

Basic Principles

Among the techniques of noninvasive brain stimulation, tDCS stands out as the method of stimulation that is one of the simplest in design. tDCS involves the flow of direct current through two sponge electrodes to the scalp. The device used in tDCS is a battery-powered current generator capable of delivering a constant electrical current flow of up to 2 mA. The device is attached to two electrodes that are soaked in saline (or water) and placed inside sponges (20–35 cm²); the sponge-electrodes are then held in place by a nonconducting rubber montage affixed around the head (see Fig. 1). Although parameters of stimulation may vary, the current density (i.e., current intensity/electrode size), duration, polarity, and location of stimulation have been shown to have important implications in the neuromodulatory outcome of stimulation (see Table 1).

Neurophysiology of tDCS: Current State of Knowledge and Controversy

tDCS is based on the application of a weak, constant direct current to the scalp via two relatively large anode and cathode electrodes. During tDCS, low-amplitude direct currents penetrate the skull to enter the brain. Although there is substantial shunting of current at the scalp, sufficient current penetrates the brain to modify the transmembrane neuronal potential (Miranda and others 2006; Wagner and others 2007) and, thus, influences the level of excitability and modulates the firing rate of individual neurons. DC currents do not induce action potentials; rather, the current appears to modulate the spontaneous neuronal activity in a polarity-dependent fashion: For example, anodal tDCS applied over the motor cortex increases the excitability of the underlying motor cortex, whereas cathodal tDCS applied over the same area decreases it (Wassermann and Grafman 2005; Nitsche and Paulus 2001). Similarly, anodal tDCS applied over the occipital cortex produces short-lasting increases in visual cortex excitability (Antal and others 2003; Lang and others 2007). Hence, tDCS is believed to deliver its effects by polarizing brain tissue, and although anodal stimulation generally increases excitability and cathodal stimulation generally reduces excitability, the direction of polarization depends strictly on the orientation of axons and dendrites in the induced electrical field (Fig. 2).

Although the polarizing effects of tDCS are generally restricted to the area under the electrodes (Nitsche and others 2003, 2004b), the functional effects appear to perpetuate beyond the immediate site of stimulation. That is, tDCS induces distant effects that go beyond the direct application of current likely via the influence of a stimulated region on other neural networks. For example, anodal tDCS of the premotor cortex increases the excitability of the ipsilateral motor cortex (Boros and others 2008); and, stimulation of the primary motor cortex has inhibitory effects on contralateral motor areas (Vines and others 2008). This supports the notion that tDCS has a functional effect not only on the underlying corticospinal excitability but also on distant neural networks (Nitsche and others 2005). Indeed, fMRI studies reveal that although tDCS has

(Text continues on page 12)
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>No. of Subjects</th>
<th>Focus of Study</th>
<th>Design</th>
<th>Electrode Placement and Polarity</th>
<th>Current Intensity</th>
<th>Session Duration</th>
<th>No. of Sessions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boggio, Khoury, and others</td>
<td>2008</td>
<td>10</td>
<td>Working memory in Parkinson’s disease patients</td>
<td>Randomized sham controlled</td>
<td>Anode over left DLPFC or left temporal cortex (35 cm²), reference CLSO</td>
<td>2.0 mA</td>
<td>30 min</td>
<td>3 sessions</td>
<td>Significant effect of stimulation condition on visual recognition memory task and post hoc analysis showed an improvement after temporal and prefrontal tDCS as compared with sham stimulation.</td>
</tr>
<tr>
<td>Mrakic-Sposta S, Marceglia S.</td>
<td>2008</td>
<td>2</td>
<td>Effects on patients with Tourette syndrome</td>
<td>Case report, sham controlled</td>
<td>Cathode over M1 (35 cm²) contralateral of the most affected side, reference over right deltoid (64 cm²)</td>
<td>2.0 mA</td>
<td>15 min</td>
<td>10 sessions</td>
<td>Cathodal tDCS over the motor areas of the cerebral cortex decreased tics in two patients with Tourette syndrome.</td>
</tr>
<tr>
<td>Antal, Lang, and others</td>
<td>2008</td>
<td>26</td>
<td>Cortico-excitability in healthy subjects and migraine patients</td>
<td>Case controlled</td>
<td>Anode or cathode over left S1 (35 cm²), reference CLSO</td>
<td>1.0 mA</td>
<td>10 min</td>
<td>3 sessions</td>
<td>5 Hz rTMS after anodal tDCS decreased amplitudes of MEPs in healthy subjects but only had a modest decrease in subjects with migraines. This indicated that short-term homeostatic plasticity is altered in patients with visual auras between attacks.</td>
</tr>
<tr>
<td>Boggio, Sultani, and others</td>
<td>2008</td>
<td>13</td>
<td>Decision making behavior</td>
<td>Double blind, sham controlled</td>
<td>Anodal or cathodal over DLPFC (35 cm²), reference over contralateral DLPFC</td>
<td>2.0 mA</td>
<td>20 min</td>
<td>2 sessions</td>
<td>Anodal left/cathodal right and anodal right/cathodal left significantly decreased alcohol craving compared with sham. And following treatment, craving could not be further increased by alcohol cues.</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>No. of Subjects</td>
<td>Focus of Study</td>
<td>Design</td>
<td>Electrode Placement and Polarity</td>
<td>Current Intensity</td>
<td>Session Duration</td>
<td>No. of Sessions</td>
<td>Results</td>
</tr>
<tr>
<td>-----------------</td>
<td>------</td>
<td>-----------------</td>
<td>--------------------</td>
<td>--------------------------------</td>
<td>=-------------------------------------------------------------------------------------------------</td>
<td>------------------</td>
<td>-----------------</td>
<td>-----------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Fregni, Liguori, and others</td>
<td>2008</td>
<td>24</td>
<td>Decision making behavior</td>
<td>Randomized double blind, sham controlled</td>
<td>Anodal over right or left DLPFC (35 cm²), reference over contralateral DLPFC (100 cm²)</td>
<td>2.0 mA</td>
<td>20 min</td>
<td>2 sessions</td>
<td>Smoking craving was significantly increased after exposure to smoking-craving cues. Stimulation of both left and right DLPFC with active, but not sham, tDCS reduced craving significantly when comparing craving at baseline and after stimulation, without and with smoking-craving cues. Craving was significantly reduced only after anode right/cathode left. Increased craving after sham and no change after anode left/cathode right. No change in subjects rating of appearance or smell of food after any condition. Calories ingested after active stimulations were significantly lower than sham. Active stimulation showed a decrease of food fixation when sham stimulation had an increase.</td>
</tr>
<tr>
<td>Fregni, Orsati, and others</td>
<td>2008</td>
<td>23</td>
<td>Decision making behavior</td>
<td>Double blind, sham controlled</td>
<td>Anode over right or left DLPFC (35 cm²), reference over the contralateral DLPFC</td>
<td>2.0 mA</td>
<td>20 min</td>
<td>2 sessions</td>
<td></td>
</tr>
</tbody>
</table>

(continued)
Table 1. (continued)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>No. of Subjects</th>
<th>Focus of Study</th>
<th>Design</th>
<th>Electrode Placement and Polarity</th>
<th>Current Intensity</th>
<th>Session Duration</th>
<th>No. of Sessions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knoch, Nitsche, and others</td>
<td>2008</td>
<td>64</td>
<td>Decision making behavior</td>
<td>Randomized sham controlled</td>
<td>Cathode over right DLPFC (35 cm²), reference CLSO (100 cm²)</td>
<td>1.5 mA</td>
<td>&lt;14 min</td>
<td>1 session</td>
<td>Cathodal stimulation reduces significantly the subjects’ propensity to punish unfair behavior.</td>
</tr>
<tr>
<td>Ferrucci, Mameli, and others</td>
<td>2008</td>
<td>10</td>
<td>Memory in Alzheimer's patients</td>
<td>Sham controlled</td>
<td>Anode and cathode temporoparietal (25 cm²) simultaneously and references over the right deltoid</td>
<td>1.5 mA</td>
<td>15 min</td>
<td>3 sessions</td>
<td>Recognition memory significantly increased after anodal. No change after sham. No changes in any condition for attention.</td>
</tr>
<tr>
<td>Boggio, Rigonatti, and others</td>
<td>2008</td>
<td>40</td>
<td>Depression</td>
<td>Double blind, sham controlled</td>
<td>Anode over DLPFC or occipital cortex (35 cm²), reference CLSO</td>
<td>2.0 mA</td>
<td>20 min</td>
<td>10 sessions</td>
<td>Stimulation of DLPFC cortex showed significantly reduced depression scores compared with occipital and sham tDCS. The beneficial effects of tDCS in the DLPFC group persisted for 1 month after the end of treatment.</td>
</tr>
<tr>
<td>Ko, Han, and others</td>
<td>2008</td>
<td>15</td>
<td>Visual neglect improvements in stroke patients</td>
<td>Double blind, sham controlled</td>
<td>Anode over right posterior parietal cortex (25 cm²), reference CLSO</td>
<td>2.0 mA</td>
<td>20 min</td>
<td>2 sessions</td>
<td>Significant improvement of percent deviation scores of the line bisect test and the number of omissions were for active stimulation only. For the letter-structure cancellation test was not significant after active or sham. Visual neglect improved.</td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>No. of Subjects</th>
<th>Focus of Study</th>
<th>Design</th>
<th>Electrode Placement and Polarity</th>
<th>Current Intensity</th>
<th>Session Duration</th>
<th>No. of Sessions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monti and others</td>
<td>2008</td>
<td>8</td>
<td>Language improvement in stroke patients</td>
<td>Sham controlled</td>
<td>Anode or cathode over Broca's area (35 cm²), reference over the shoulder, or cathode over occipital cortex, same reference</td>
<td>2.0 mA</td>
<td>10 min</td>
<td>4 sessions</td>
<td>Cathodal stimulation significantly improved the accuracy of the picture-naming task, anodal and sham produced no response.</td>
</tr>
<tr>
<td>Boggio, Bermpohl, and others</td>
<td>2007</td>
<td>26</td>
<td>Working memory in depressive patients</td>
<td>Sham controlled</td>
<td>Anode over left DLPFC (35 cm²) or occipital cortex, reference CLSO</td>
<td>2.0 mA</td>
<td>20 min</td>
<td>10 sessions</td>
<td>Anodal stimulation of the left DLPFC was the only condition that induced a significant improvement in task performance as shown by the increase in the number of correct responses. This effect was specific for figures with positive emotional content.</td>
</tr>
<tr>
<td>Boggio, Nunes, and others</td>
<td>2007</td>
<td>9</td>
<td>Motor function in stroke patients</td>
<td>Experiment 1: double blind, sham controlled; experiment 2: open label</td>
<td>(1) Anode over the affected M1 (35 cm²), reference CLSO; (2) cathode over the unaffected M1 (35 cm²) and same reference</td>
<td>1.0 mA</td>
<td>20 min</td>
<td>(1) 12 sessions</td>
<td>Cathodal stimulation of the unaffected hemisphere and anodal of the affected one showed significant motor improvement and there was no significant difference between them ($P = .56$). For experiment 2 a significance in effect of time was found. The effect of 5 consecutive treatments lasted 2 weeks.</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>No. of Subjects</td>
<td>Focus of Study</td>
<td>Design</td>
<td>Electrode Placement and Polarity</td>
<td>Current Intensity</td>
<td>Session Duration</td>
<td>No. of Sessions</td>
<td>Results</td>
</tr>
<tr>
<td>------------------------</td>
<td>------</td>
<td>-----------------</td>
<td>----------------------------------------------</td>
<td>-------------------------------</td>
<td>------------------------------------------------------------------------</td>
<td>------------------</td>
<td>------------------</td>
<td>-----------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Hesse, Werner, and others</td>
<td>2007</td>
<td>10</td>
<td>Motor function in stroke patients</td>
<td>Open label</td>
<td>Anode over affected M1 (35 cm²), reference CLSO</td>
<td>1.5 mA</td>
<td>7 min</td>
<td>30 sessions</td>
<td>Fugl-Meyer motor scores improved significantly over time. Three patients profited markedly, starting from an initial score of 6, 10, and 11, they gained +22, +39, and +37 FM scores, respectively. The other 7 patients either did not improve or gained no more than 5 FM scores.</td>
</tr>
<tr>
<td>Huey, Probasco, and others</td>
<td>2007</td>
<td>10</td>
<td>Effects of tDCS on verbal fluency of patients with dementia</td>
<td>Double blind, sham controlled</td>
<td>Anode over left M1 (25 cm²), reference CLSO</td>
<td>2.0 mA</td>
<td>20 min</td>
<td>2 sessions (active or sham)</td>
<td>There was no significant improvement in verbal fluency in active stimulation relative to sham. There was a significant effect of treatment, independent of type, apparently related to practice.</td>
</tr>
<tr>
<td>Roizenblatt, Fregni, and others</td>
<td>2007</td>
<td>36</td>
<td>Fibromyalgia</td>
<td>Sham controlled</td>
<td>Anode over left M1 or left DLPFC (35 cm²), reference CLSO</td>
<td>2.0 mA</td>
<td>20 min</td>
<td>5 sessions</td>
<td>M1 stimulation significantly increased sleep efficiency and decreased arousals. DLPFC stimulation significantly decreased sleep efficiency, increased rapid eye movement (REM) and sleep latency.</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>No. of Subjects</td>
<td>Focus of Study</td>
<td>Design</td>
<td>Electrode Placement and Polarity</td>
<td>Current Intensity</td>
<td>Session Duration</td>
<td>No. of Sessions</td>
<td>Results</td>
</tr>
<tr>
<td>---------------------</td>
<td>------</td>
<td>-----------------</td>
<td>-------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
<td>---------------------------------</td>
<td>-------------------</td>
<td>------------------</td>
<td>-----------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Quartarone, Lang, and others</td>
<td>2007</td>
<td>16</td>
<td>Effects of tDCS on patients with amyotrophic lateral sclerosis (ALS)</td>
<td>Pseudo-randomized for anodal and cathodal stimulation</td>
<td>Anode or cathodal over left M1 (35 cm²), reference CLSO</td>
<td>1.0 mA</td>
<td>7 min</td>
<td>2 sessions</td>
<td>The healthy volunteers showed a transient polarity-specific change in corticospinal excitability of about ±45%, anodal had facilitatory effects and cathodal had inhibitory effects. For subjects with ALS no change was induced by either cathodal or anodal tDCS.</td>
</tr>
<tr>
<td>Fregni, Marcondes, and others</td>
<td>2006</td>
<td>7</td>
<td>Effects of tDCS in chronic tinnitus</td>
<td>Randomized sham controlled</td>
<td>Anode or cathode over left temporal area (35 cm²), reference over CLSO</td>
<td>1.0 mA</td>
<td>3 min</td>
<td>6 sessions (2 of each: anodal, cathodal, and sham)</td>
<td>Anodal tDCS of LTA resulted in a significant reduction of tinnitus.</td>
</tr>
<tr>
<td>Boggio, Ferrucci, and others</td>
<td>2006</td>
<td>18</td>
<td>Working memory in patients with Parkinson's disease</td>
<td>Single blind, sham controlled</td>
<td>Anode over left DLPFC (35 cm²) or M1, reference CLSO</td>
<td>1 or 2 mA</td>
<td>20 min</td>
<td>3 sessions (sham, M1, or DLPFC)</td>
<td>Reaction time was significantly decreased in anodal stimulation of M1 but not for DLPFC or sham. For DLPFC the number of correct responses was significantly higher than baseline and significantly different than sham stimulation and M1 stimulation. Although M1 stimulation was associated with an increase in the correct responses and a decrease in the errors it was not significantly different when compared with baseline and sham stimulation.</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>No. of Subjects</td>
<td>Focus of Study</td>
<td>Design</td>
<td>Electrode Placement and Polarity</td>
<td>Current Intensity</td>
<td>Session Duration</td>
<td>No. of Sessions</td>
<td>Results</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------</td>
<td>-----------------</td>
<td>--------------------------</td>
<td>---------------------------------------</td>
<td>----------------------------------</td>
<td>-------------------</td>
<td>------------------</td>
<td>----------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Fregni, Boggio, and others</td>
<td>2006</td>
<td>10</td>
<td>Depression</td>
<td>Double blind, sham controlled</td>
<td>Anode over left DLPFC (35 cm²), reference CLSO</td>
<td>1.0 mA</td>
<td>20 min</td>
<td>5 sessions</td>
<td>Patients that received active stimulation had more of a decrease in Hamilton Depression Rating Scale scores and Beck Depression Inventory Score from baseline than those patients who received sham.</td>
</tr>
<tr>
<td>Hummel, Voller, and others</td>
<td>2006</td>
<td>11</td>
<td>Motor function in stroke patients</td>
<td>Double blind, sham controlled</td>
<td>Anode over M1 (25 cm²), reference CLSO</td>
<td>1.0 mA</td>
<td>20 min</td>
<td>2 sessions (active and sham)</td>
<td>Reaction time had a significant reduction with tDCS (and a nonsignificant trend to lengthening with sham).</td>
</tr>
<tr>
<td>Fregni, Gimenes, and others</td>
<td>2006</td>
<td>32</td>
<td>Fibromyalgia</td>
<td>Sham controlled</td>
<td>Anode over left M1 or DLPFC (35 cm²), reference CLSO</td>
<td>2.0 mA</td>
<td>20 min</td>
<td>5 sessions</td>
<td>Anodal stimulation of M1 had significant improvements in pain compared with sham and stimulation of DLPFC. Improvement decreased but still was significant 3 weeks after stimulation. A small positive impact on quality of life was observed among patients who received anodal M1 stimulation. Cognitive changes were the same over the 3 groups.</td>
</tr>
<tr>
<td>Fregni, Thome-Souza, and others [1]</td>
<td>2006</td>
<td>19</td>
<td>Epilepsy</td>
<td>Sham controlled</td>
<td>Cathode over the epileogenic focus (35 cm²) and anode over the epileogenic focus</td>
<td>1.0 mA</td>
<td>20 min</td>
<td>1 session</td>
<td>Active compared with sham was associated with a significant reduction in the number of epileptiform. A trend ($P = .06$) was noted for decreases in seizure frequency after active compared with sham.</td>
</tr>
</tbody>
</table>
Table 1. (continued)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>No. of Subjects</th>
<th>Focus of Study</th>
<th>Design</th>
<th>Electrode Placement and Polarity</th>
<th>Current Intensity</th>
<th>Session Duration</th>
<th>No. of Sessions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fregni, Boggio, and others [2]</td>
<td>2006</td>
<td>17</td>
<td>Effects of tDCS on patients with Parkinson’s disease</td>
<td>Double blind, sham controlled</td>
<td>Anode over left M1 OR DLPFC (35 cm²), reference CLSO</td>
<td>1 mA</td>
<td>20 min</td>
<td>2 sessions (active and sham)</td>
<td>Anodal stimulation of M1 was associated with a significant improvement of motor function compared with sham stimulation in the Unified Parkinson’s Disease Rating Scale and simple reaction time. This effect was not observed for cathodal stimulation of M1 or anodal stimulation of DLPFC.</td>
</tr>
<tr>
<td>Hummel and Cohen</td>
<td>2005</td>
<td>1</td>
<td>Motor function in stroke patient</td>
<td>Double blind, sham controlled</td>
<td>Anode over affected M1 (25 cm²) and reference over contralateral supraorbital area</td>
<td>1.0 mA</td>
<td>20 min</td>
<td>3 sessions (1 sham, 2 active)</td>
<td>Active but not sham applied in a double-blind protocol to motor regions of the affected hemisphere led to improvements in pinch in the paretic hand that outlasted the stimulation period for at least 40 min.</td>
</tr>
</tbody>
</table>

Note: The table is a review of studies that investigate the use of low-intensity (subthreshold) constant DC stimulation with respect to clinical outcomes. Search criteria was published in English within the last 10 years, as indexed on Medline or Scopus using the following key words: transcranial direct current stimulation; tDCS; brain polarization; brain, electrical stimulation; brain, direct current. CLSO = contralateral supraorbital area. DLPFC = dorsolateral prefrontal cortex; LTA = left temporal area; MEPs = motor evoked potentials; rTMS = repetitive transcranial magnetic stimulation. 10–20 EEG system. Reference and active electrodes are of the same size unless otherwise indicated.
The most activating effect on the underlying cortex (Kwon and others 2008), the stimulation provokes sustained and widespread changes in other regions of the brain (Lang and others 2005). EEG studies support these findings showing that stimulation of a certain area (e.g., frontal) induces changes to oscillatory activity that are synchronous throughout the brain (Marshall and others 2004; Ardolino and others 2005). Hence, this evidence suggests that the effects of DC stimulation are site specific but not site limited; that is, stimulation of one area will likely have effects on other areas, most likely via networks of interneuronal circuits (Lefaucheur 2008). This phenomenon is not surprising given the neuroanatomic complexity of the brain, but it raises some interesting questions as to 1) how the effects are transmitted, and 2) whether the observed clinical effects (e.g., pain, depression alleviation) are mediated primarily through the area of the cortex being stimulated or secondarily via activation or inhibition of other cortical and/or subcortical structures (Boggio and others 2008, 2009).

Although it is generally well agreed that DC stimulation can affect cortical excitability, there is controversy as to whether the observed changes are the result of alterations in membrane excitability, synaptic transmission, or other molecular effects. That is, does tDCS render its effect by directly changing the physiology of the neuronal membrane (thereby making a given neural network more or less likely to reach threshold); or, does tDCS function to induce diffuse local changes (such as inducing ionic shifts) throughout the brain that results in a facilitation or inhibition of spontaneous neuronal activity indirectly (Ardolino and others 2005)? On a molecular level, many additional questions remain: Can tDCS indeed change ion conductance at the neuronal membrane, and if so, how? Perhaps tDCS induces the migration and collection of transmembrane proteins by establishing a prolonged constant electric field, but it is also possible that stimulation causes steric and conformational changes in these proteins inducing functional effects (Ardolino and others 2005). Are the long-term effects of tDCS indeed mediated by the activation of N-methyl-d-aspartate (NMDA) channels as previously proposed (Nitsche and others 2004a), and, if so, could we then induce cortical effects that persist for weeks and months with repeated stimulation? Further mechanistic studies are needed to increase our understanding of the neurophysiological basis of tDCS.

**Noninvasive Brain Stimulation with Low-Intensity Pulsed and Alternating Current**

**Basic Principles**

Given the remarkable effects of transcranial stimulation with low-intensity constant direct current (tDCS), the use of low-intensity nonconstant current may also prove to be an attractive option. Nonconstant current...
can be delivered with pulses of unidirectional current in rectangular waves (intensity rapidly increased to a certain amplitude, held at the peak without change, and then interrupted by zero current) or sinusoidal waves (intensity constantly varies as a function of time), or modifications thereof. Moreover, nonconstant current can be delivered with unidirectional current (in which pulses share the same polarity) or AC (in which the pulses of current alternate with opposite amplitude). Indeed, stimulation with nonconstant current is the preferred parameter of neural stimulation in other domains of nervous system stimulation: It is the method used in deep brain stimulation, motor cortex stimulation, spinal cord stimulation, transcutaneous nerve stimulation, vagal nerve stimulation, TMS, and ECT. Of the variety of methods of low-intensity nonconstant current that have been explored, here we will discuss the few specific methods of AC stimulation that have been purported to have clinical effects: cranial electrotherapy stimulation (CES), transcutaneous electrical stimulation (TCES) with Limoge’s current, transcranial electrical stimulation (TES) with Lebedev’s current, and transcranial alternating current stimulation (tACS). Of note, although AC is applied to the head in these circumstances, the current may or may not be delivered directly to the underlying brain structures and thus the term “transcranial” may not apply; we therefore select the term “cranial” AC stimulation to include applications of low-intensity AC in this context. Indeed, CES might more accurately be considered a form of peripheral nerve stimulation.

Methods of AC Stimulation

With respect to the application of low-intensity AC, there are several methods of AC stimulation that have been tried in the past and are being explored at the present. Because these methods are significantly different regarding parameters of stimulation, we will discuss them separately, as below.

CES is a form of AC stimulation that involves the application of current to infra- or supra-auricular structures (e.g., the ear lobes, mastoid processes, zygomatic arches, or maxillo-occipital junction; Fig. 4). CES is a nonstandardized and often indistinct method of delivering cranial AC stimulation; indeed many studies cite the method of stimulation simply as “cranial electrotherapy stimulation” without identifying the specific site or other parameters of stimulation (e.g., duration, current density, intensity, electrode size) calling into question existing reviews of this method. Even so, CES has been suggested to be effective in the treatment of anxiety, depression, stress, and insomnia (Kirsch and Smith 2004; Smith 2007), and the following parameters of stimulation have been reported: frequency (0.5 Hz to 167 kHz), intensity (100 µA to 4 mA), and duration of stimulation (5 min to 6 consecutive days). Of note, although AC is applied to the head in these circumstances, the current may or may not be delivered directly to the underlying brain structures and thus the term “transcranial” may not apply; we therefore select the term “cranial” AC stimulation to include applications of low-intensity AC in this context. Indeed, CES might more accurately be considered a form of peripheral nerve stimulation.

The term TCES (“transcutaneous electrical stimulation”) is mostly associated with a very specific protocol of AC stimulation, called Limoge’s current, in which current is applied by utilizing three cutaneous electrodes: one negative electrode (cathode) that is placed between the eyebrows and two positive electrodes (anode) that are placed in the retromastoid region. Stimulation carries a voltage (peak to peak) of 30 to 35 V and an average intensity of 2 mA. In the application of “Limoge’s current,” wave trains are composed of successive impulse waves of a particular shape: one positive impulse (S1) of high intensity and short duration, followed by a negative impulse (S2) of weak intensity and long duration (see Fig. 5). The impulse waves are delivered at 166 kHz bursts (4 mS “ON” + 8 mS “OFF”). This form of transcranial stimulation has been suggested to decrease the amount of narcotics required to maintain anesthesia during surgical procedures (Limoge and others 1999).
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n</th>
<th>Focus of Study</th>
<th>Design</th>
<th>Electrode Placement</th>
<th>Current Intensity</th>
<th>Frequency</th>
<th>Session Duration</th>
<th>Treatment Duration</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kanai and others</td>
<td>2008</td>
<td>8</td>
<td>Visual phosphene induction in healthy subjects</td>
<td>Randomized, single blind, condition control</td>
<td>Occipital cortex (12 cm²) and vertex (54 cm²)</td>
<td>250 µA to 1500 µA</td>
<td>5–30 Hz</td>
<td>60–90 min</td>
<td>5–10 sec per trial, each separated by 30 sec</td>
<td>Induction of phosphenes: 20 Hz most effective in light, 10 Hz in dark.</td>
</tr>
<tr>
<td>Antal and others</td>
<td>2008</td>
<td>36</td>
<td>Cortical excitability in healthy subjects</td>
<td>Randomized double blind sham control</td>
<td>Left M1 (size of 16 cm²) and supraorbital (50 cm²)</td>
<td>400 µA</td>
<td>1, 10, 30, 45 Hz</td>
<td>5–10 min</td>
<td>—</td>
<td>No significant interactions, except for improvement in implicit motor learning task with 10 Hz frequency.</td>
</tr>
<tr>
<td>Bystritsky and others</td>
<td>2008</td>
<td>12</td>
<td>Effects in patients with generalized anxiety disorder diagnosis</td>
<td>Open label</td>
<td>Earlobe</td>
<td>Below perception threshold (all below 300 µA)</td>
<td>0.5 Hz</td>
<td>60 min/day</td>
<td>6 weeks</td>
<td>50% of the patients met the criteria response for improvement in anxiety.</td>
</tr>
<tr>
<td>Tan and others</td>
<td>2006</td>
<td>40</td>
<td>Pain in spinal cord injury patients</td>
<td>Randomized double blind placebo control and an open label phase</td>
<td>Earlobe</td>
<td>100 µA</td>
<td>—</td>
<td>60 min/day</td>
<td>21 days</td>
<td>No significant difference between groups regarding pre- and posttreatment means, but significant difference in the average pain change between groups in the daily ratings.</td>
</tr>
<tr>
<td>Scherder and others</td>
<td>2006</td>
<td>20</td>
<td>Rest activity rhythm and cortisol levels in AD patients</td>
<td>Randomized double blind sham-control</td>
<td>Earlobe</td>
<td>10–600 µA</td>
<td>100 Hz</td>
<td>30 min/day</td>
<td>5 days/week for 6 weeks</td>
<td>No interaction between treatment cortisol levels or rest-activity rhythm.</td>
</tr>
<tr>
<td>Scherder and others</td>
<td>2006</td>
<td>21</td>
<td>Cognition, mood and behavior in AD patients</td>
<td>Randomized double blind sham control</td>
<td>Earlobe</td>
<td>10–600 µA</td>
<td>100 Hz</td>
<td>30 min/day</td>
<td>5 days/week for 6 weeks</td>
<td>No significant difference in any of the outcomes.</td>
</tr>
<tr>
<td>Childs and others</td>
<td>2005</td>
<td>9</td>
<td>Effects on patients with aggressive behavior</td>
<td>Open label</td>
<td>Earlobe</td>
<td>Below perception threshold (max 600 µA)</td>
<td>0.5–100 Hz</td>
<td>60 min/day or 45 min × 2/ day</td>
<td>Daily for 3 months</td>
<td>59% decrease in aggressive episodes.</td>
</tr>
<tr>
<td>Markina</td>
<td>2004</td>
<td>90</td>
<td>Effects on adaptive</td>
<td>Comparison of measurements</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>20 min/day</td>
<td>10 days</td>
<td>Trancranial electrostimulation</td>
</tr>
</tbody>
</table>

(continued)
Table 2. (continued)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n</th>
<th>Focus of Study</th>
<th>Design</th>
<th>Electrode Placement</th>
<th>Current Intensity</th>
<th>Frequency</th>
<th>Session Duration</th>
<th>Treatment Duration</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capel and others</td>
<td>2003</td>
<td>30</td>
<td>Pain in subjects with spinal cord injury</td>
<td>Randomized double blind placebo control</td>
<td>Earlobe</td>
<td>Pulses with positive amplitude of 12 µA</td>
<td>50 Hz</td>
<td>53 min × 2/day</td>
<td>4 days</td>
<td>Significant decrease in pain scores as compared with sham.</td>
</tr>
<tr>
<td>Gabis and others</td>
<td>2003</td>
<td>20</td>
<td>Pain in β-endorphine subjects with chronic back pain</td>
<td>Randomized double blind placebo control</td>
<td>Mastoids</td>
<td>4 mA (sham was 0.75 mA)</td>
<td>77 Hz</td>
<td>30 min/day</td>
<td>8 days</td>
<td>No significant difference between treatment in pain scores, but significant difference in β-endorphin levels.</td>
</tr>
<tr>
<td>Scherder and others</td>
<td>2002</td>
<td>18</td>
<td>Rest activity rhythm and cortisol levels in AD patients</td>
<td>Randomized double blind sham control</td>
<td>Earlobe</td>
<td>10–600 µA</td>
<td>0.5 Hz</td>
<td>30 min/day</td>
<td>5 days/week for 6 weeks</td>
<td>No interaction between treatment cortisol levels or rest-activity rhythm.</td>
</tr>
<tr>
<td>Lichtbroun and others</td>
<td>2001</td>
<td>60</td>
<td>Cognition and behavior in AD</td>
<td>Randomized double blind sham control and open label phase control</td>
<td>Earlobe</td>
<td>100 µA</td>
<td>0.5 Hz</td>
<td>60 min/day</td>
<td>3 weeks</td>
<td>Significant improvement of the treated group as compared with sham.</td>
</tr>
<tr>
<td>Schroeder and others</td>
<td>2001</td>
<td>20</td>
<td>EEG alterations in HS</td>
<td>Randomized double blind sham control</td>
<td>Earlobe</td>
<td>10–100 µA</td>
<td>0.5 and 100 Hz</td>
<td>20 min/session (sham, 0.5–100 Hz)</td>
<td>3 sessions</td>
<td>Relative to sham control, 0.5, and 100 Hz caused the alpha band mean frequency to shift downward. Additionally, 100 Hz also caused a decrease of the alpha band median frequency and beta band power fraction.</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>n</td>
<td>Focus of Study</td>
<td>Design</td>
<td>Electrode Placement</td>
<td>Current Intensity</td>
<td>Frequency</td>
<td>Session Duration</td>
<td>Treatment Duration</td>
<td>Results</td>
</tr>
<tr>
<td>---------------------</td>
<td>------</td>
<td>----</td>
<td>--------------------------</td>
<td>---------------------------------------------</td>
<td>----------------------</td>
<td>------------------</td>
<td>-----------</td>
<td>------------------</td>
<td>-------------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>Southworth and others</td>
<td>1999</td>
<td>52</td>
<td>Memory and attention in HS</td>
<td>Randomized double-blind placebo control</td>
<td>Temples</td>
<td>—</td>
<td>15 kHz</td>
<td>20 min</td>
<td>1 session</td>
<td>Attention improved significantly in comparison with sham stimulation.</td>
</tr>
</tbody>
</table>

Note: The table is a review of studies that investigate the use of low-intensity (subthreshold) AC stimulation with respect to clinical outcomes. Search criteria—published in English within the last 10 years, as indexed on Medline or Scopus using the following key words: transcranial alternating current stimulation; cranial electrotherapy stimulation; transcutaneous electrical stimulation; brain, electrical stimulation; brain, alternating current. AD = Alzheimer's disease; EEG = electroencephalogram; HS = healthy subjects.
Lebedev describes a method of transcranial electrical stimulation that is based on electrode positions similar to Limoge, but instead includes a combination of AC and DC current at a 2:1 ratio. A pulse train of AC is delivered at the optimal frequency of 77.5 Hz for 3.5 to 4.0 msec separated from the next train by 8 msec. Two trains of AC stimulation are followed by a 4-msec stream of constant DC. Lebedev’s current has been suggested to be effective for the treatment of stress and affective disturbances of human psychophysiological status (Lebedev and others 2002).

Recently, Antal and others have used alternating currents with a similar montage as in tDCS and appropriately referred to it as transcranial alternating current stimulation (tACS; Antal and others 2008). In their experiments, electrical stimulation was delivered with the same type of device used to deliver tDCS, that is, a battery-driven constant-current stimulator (NeuroConn GmbH, Ilmenau, Germany) with conductive-rubber electrodes, enclosed in two saline-soaked sponges affixed on the scalp with elastic bands. The stimulation electrode was placed over the left motor cortex, and the reference electrode was placed over the contralateral orbit. tACS was applied for 2 and 5 min with a current intensity of 250 to 400 µA using a 16-cm² electrode (current density = 25 µA/cm²) at the following frequencies: 1, 10, 15, 30, and 45 Hz (Antal and others 2008). Antal and colleagues were unable to show robust effects on cortical excitability, but they did show that 5-min tACS at 10 Hz applied at the motor cortex could improve implicit motor learning.

Similarly, Kanai and colleagues have more recently applied tACS to the visual cortex at 5 to 30 Hz and 250 µA to 1000 µA and induced visual phosphenes. This group demonstrated that stimulation over the occipital cortex could induce perception of continuously flickering light; these effects were most prominent at 1 mA and, interestingly, the AC stimulation had differential effects in a light versus dark room. tACS was most effective in inducing phosphenes at 20 Hz (beta frequency range) when applied in an illuminated room and 10 Hz (alpha frequency range) in darkness. In this way, Kanai and colleagues showed that tACS could indeed be used to interact with ongoing oscillatory activity (Kanai and others 2008).

**Neurophysiology of Cranial AC Stimulation: Current State of Knowledge and Controversy**

As with the technique of tDCS, one of the main conceptual issues for the understanding of cranial AC stimulation is whether the applied electric current can overcome the resistance of skin, soft tissues, and the skull to penetrate the brain. Although part of the current...
is usually shunted through skin, a significant amount of current can be injected into the brain if the electrodes are positioned adequately. An electrophysiologic mathematical model of cranial AC stimulation shows that, with a 1-mA stimulus applied via standard electrodes behind the ear, the maximum injected current density is about 5 µA/cm² at a radius of 13.30 mm (thalamic area) of the model (Ferdjallah and others 1996). This suggests that, indeed, although the vast majority of the applied current is diffused across the scalp, a small fraction of the stimulating current can penetrate brain tissue and even reach deep brain structures, including the thalamic nuclei (Ferdjallah and others 1996). In addition, when CES was applied to the head of primates, it was found that 42% of the current applied externally actually penetrated throughout the entire brain, canalizing especially along the limbic system (Jarzembski 1970; Kirsch and Smith 2004). In addition, the recent modeling studies for DC stimulation (given the limitations inherent to the method of modeling studies and also given that electrode positions and sizes are different) can also be used to show that electric currents can reach the brain tissue (Miranda and others 2006; Wagner and others 2007). Therefore, low-intensity cranial AC stimulation can indeed penetrate the scalp to deliver AC to brain tissue. Although it is conceivable that electrical stimulation with small currents can reach the cortex, the subsequent critical issue is whether a subthreshold, very small current can induce biological changes. It is known that suprathreshold AC stimulation does induce changes in neuronal activity and can, for instance, induce the phenomenon of LTP and LTD (Habib and Dringenberg 2009). However, for small currents, this is not clear. Although DC currents also use small currents, the effects of this technique are based on cumulative effects affecting

Figure 5. Main characteristics of Limoge and Lebedev current stimulation. a, Wave trains are composed of successive impulse waves of a particular shape: one positive impulse (S1) of high intensity and short duration, followed by a negative impulse (S2) of weak intensity and long duration. The high-frequency current is regularly interrupted by a low-frequency cycle (4 mS "ON" + 8 mS "OFF"). b, Headset positioning of electrodes in Limoge and Lebedev current stimulation (adapted with permission from Limoge and others 1999).
the area under the constant gradient of voltage. We therefore review evidence regarding the biological effects of low-intensity cranial AC according to different methods to investigate brain activity (Fig. 6).

**Cortical excitability changes as indexed by single pulse TMS.** Antal and others (2008) recently explored whether transcranial AC stimulation applied for 5 min at the motor cortex could significantly modulate cortical excitability. Using a current density of 25 µA/cm² at 1, 10, 15, 30, and 45 Hz, this group showed that AC stimulation did not result in significant changes to cortical excitability as measured by TMS evoked motor potentials. Although the results of this study may be restricted to the parameters of stimulation investigated, these findings suggest that unlike tDCS and repetitive TMS, the effects of cranial AC stimulation might not be due to a modulation of local cortical excitability (Antal and others 2008).

**Electrical activity changes as indexed by EEG.** Most studies confirm significant EEG changes during cranial stimulation with low-intensity AC. An EEG study by McKenzie and others (1971) found that one 30-min session of cranial AC stimulation each day for five days yielded increases in the amplitudes of slower EEG frequencies with increased alpha wave (8–12 Hz) activity (McKenzie and others 1971). More recently, Schroeder and Barr (2001) measured EEG activity during sham and AC stimulation and showed increases in low alpha (8–12 Hz) and high theta (3–8 Hz) activity; these findings were significant even when controlled for AC stimulation induced electrical noise. Even so, EEG recordings before and after transcranial AC stimulation of the motor cortex (400 µA; 5 min; 1, 10, and 45 Hz) failed to show a difference in effect before and after stimulation (Antal and others 2008). Therefore, cranial AC stimulation may alter EEG patterns toward more relaxed states during stimulation, but current evidence suggests that it is unlikely to leave a lasting effect on EEG patterns at the completion of stimulation; and, in addition, these effects may be highly dependent on the specific parameters of stimulation investigated.

**Biochemical changes—neurotransmitter and endorphin release.** Several studies suggest that AC stimulation may be associated with changes in neurotransmitters and endorphin release. In this context, subthreshold
stimulation induced by AC stimulation would indeed cause significant changes in the nervous system electrical activity. Briones and others demonstrated changes in urinary free catecholamines and 17-ketosteroids after stimulation (Briones and Rosenthal 1973); Pozos and others showed that cranial AC stimulation can be as effective as L-dopa (and both better than no treatment) in accelerating the re-equilibrium of the adrenergic-cholinergic balance in the canine brain after administration of reserpine and physostigmine (Kirsch and Smith 2004). In another study, presynaptic membranes were analyzed before, during, and following cranial AC stimulation of four squirrel monkeys (Kirsch and Smith 2004). The results showed that the number of vesicles declined when stimulation first began, increased after five minutes of stimulation, and returned toward normal shortly after cessation of stimulation. Some authors collectively use this evidence to speculate that some forms of cranial AC stimulation may directly engage serotonin-releasing raphe nuclei, norepinephrine-releasing locus ceruleus, or the cholinergic laterodorsal tegmental and pediculo-pontine nuclei of the brainstem (Kirsch 2002; Giordano 2006); however, we believe that there is not enough evidence to fully support this notion. Interestingly, Limoge and others demonstrate significant changes to blood plasma and CSF levels of endorphins during cranial AC stimulation, and they report that naloxone antagonized the analgesic effects of stimulation (Limoge and others 1999). Although it is not possible to determine whether neurotransmitter and endorphin hormone changes are directly or indirectly related to AC stimulation of the brain, these studies do suggest that there is at least an association between cranial AC stimulation and neurotransmitters release. Even so, current evidence is inadequate to suggest that these effects are of central origin, because neurotransmitter changes may also be induced by nonspecific peripheral effects.

**Interruption of on-going cortical activity (i.e., introducing cortical noise).** It is possible that stimulation of the brain with a constantly varying electrical force could induce noise that would interfere with ongoing oscillations in the brain. Indeed, evidence from in vitro studies of rat brain slices shows that high frequency (50–200 Hz) sinusoidal stimulation with AC suppresses activity in both cell bodies and axons (Jensen and Durand 2007), demonstrating a disruptive effect of stimulation on basic neural processing. In addition, low-frequency (0.9 Hz) alternating electric cortical stimulation applied directly to epileptogenic foci has been shown to decrease interictal and ictal activity in human epilepsy, further supporting the notion that nonconstant stimulation can interrupt neural activity (Yamamoto and others 2006). Similarly, pulsed stimulation applied over the lateral prefrontal cortex during a working memory task (15 sec on/15 sec off) was shown to impair central nervous processing related to response selection and preparation in working memory (Marshall and others 2005), further suggesting that it is possible for pulsed current to have an interrupting effect on nervous system function.

**Secondary effects via peripheral nerve stimulation.** Finally, the effects of cranial AC stimulation might be due to a primary effect on the peripheral nervous system that is secondarily transmitted to the CNS. Studies of transcranial electrostimulation in rats suggest that peripheral craniospinal sensory nerves play a critical role in mediating the anti-nociceptive action of pulsed electrical stimulation (Nekhendzy and others 2006). In this study, antinociceptive effects of stimulation were blocked with the application of local anesthetic injected under the stimulation electrodes. This suggests that the effects of low-intensity cranial AC stimulation may be mediated through the activation of brainstem centers (i.e., trigeminal subnucleus caudalis and wide-dynamic range neurons of the solitary nucleus) via stimulation of peripheral cranial (CN V1–V3 and VII) and craniospinal nerves (C1–C3). Similar results have been reported in studies of scalp stimulation with rhesus monkeys (Kano and others 1976). Therefore, cranial AC stimulation may function via a mechanism similar to TENS units (transcutaneous electrical nerve stimulation; devices used to help control pain via application of electric current to peripheral nerves).

**Noninvasive Cranial Stimulation with Low-Intensity Electrical Currents—What Have We Learned So Far?**

The field of cranial electrical stimulation is developing rapidly—especially with the new attention focused on the techniques of neuromodulation for the treatment of neuropsychiatric diseases. Although these techniques have been used for many years, the recent increased interest in these methods have provided new insight that were discussed in this review and we summarize them in seven points: 1) recent studies using new techniques to index cortical activity (such as single-pulse TMS) have shown that parameters of stimulation such as duration of stimulation and electrode montage play a critical role for the effects of these methods of brain stimulation; 2) modeling and animal studies have shown that electrical currents can be induced in the brain using cranial methods of brain stimulation, and preliminary use in humans has shown that these techniques are associated with relatively minor adverse effects; 3) techniques of cranial electrical stimulation induce changes in central nervous system activation (as indexed by changes in EEG, neurotransmitter...
release, and cortical excitability); 4) it is not clear whether the effects of cranial electrical stimulation are specifically due to currents that are induced in the brain as opposed to the modification of peripheral nerve activity that are secondarily transmitted to the brain; 5) DC stimulation has been shown to polarize brain tissue with long-lasting, site-specific effects on CNS activity; and 6) the mechanism of AC stimulation has been understudied; and 7), although limitations certainly exist for the use of cranial electrical stimulation, some studies show encouraging results that at the very least suggest that further research in this area is needed.

Summary

Noninvasive stimulation of the brain with low-intensity direct and alternating currents have both been associated with significant clinical effects, but results from various groups are often mixed, and many studies are limited by small sample sizes and experimental design. tDCS has been shown to induce long-lasting shifts in the polarity of the underlying cortex resulting in large changes in cortical excitability. In tDCS, the effect of weak currents delivered to the brain may be compensated for by the cumulative time-dependent effects of unidirectional polarizing stimulation (Nitsche and Paulus 2001; Paulus 2003). Hence, tDCS is believed to deliver its effects by polarizing brain tissue, and although anodal stimulation generally increases excitability and cathodal stimulation generally reduces excitability, the direction of polarization depends strictly on the orientation of axons and dendrites in the induced electrical field. tDCS can induce effects beyond the immediate site of stimulation because the effects of DC stimulation are perpetuated throughout the brain via networks of interneuronal circuits. On the other hand, recent evidence suggests that the effects of cranial AC stimulation may not be due to a modulation of local cortical excitability (Antal and others 2008): Because the direction of current is constantly changing with AC stimulation, the possibility of polarization with a weak current becomes unlikely. Even so, cranial AC stimulation may function by 1) inducing synchronous changes in brain activity (as indexed by EEG); 2) altering the release of synaptic vesicles (i.e., stimulating neurotransmitter or endorphin release); 3) interrupting ongoing cortical activity by introducing cortical noise; or 4) via secondary effects of peripheral craniospinal nerve stimulation. Despite the differing proposed mechanisms of action, preliminary small studies suggest that both techniques show promising results and should be explored further. Future studies should target an understanding of the mechanisms or neurophysiology of these methods of neuromodulation in addition to well-controlled and well-designed clinical studies also addressing the mechanisms of action.

References


For reprints and permissions queries, please visit SAGE’s Web site at http://www.sagepub.com/journalspermissions.nav.