Electrotherapies in Modern Medicine
10th Annual Nurturing Developing Minds Conference

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Greenville Health System
Conflict of Interests

- Neuronetics (TMS platform), Neuronetrix Incorporated, Clearly Present Foundation
- Pfizer, Eisai, Nycomed Amersham, Aventis Pasteur Limited, Medvantis Medical Service
- Council of Health Care Advisors for the Gerson Lehrman Group
- Royalties: Springer, Nova, Taylor and Francis, John Wiley
The Hippocratic Corpus (450-350 B.C.)

In ancient Greece disease was thought to be caused by a preponderance of one of the 4 bodily humors each one also corresponding to the 4 temperaments, i.e., sanguine, melancholic, phlegmatic and choleric.

<table>
<thead>
<tr>
<th>Fluid</th>
<th>Type</th>
<th>Element</th>
<th>Color</th>
<th>Taste</th>
<th>Personality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yellow bile</td>
<td>Choleric</td>
<td>Fire</td>
<td>yellow orange</td>
<td>bitter</td>
<td>Extrovert: aggressive, decisive, ambitious, quick-tempered, cunning</td>
</tr>
<tr>
<td>Black bile</td>
<td>Melancholic</td>
<td>Earth</td>
<td>black</td>
<td>sour</td>
<td>Introvert: idealistic, introspective, depressed,</td>
</tr>
<tr>
<td>Blood</td>
<td>Sanguine</td>
<td>Air</td>
<td>red</td>
<td>sweet</td>
<td>Extrovert: fun loving, carefree, optimistic, kind, caring, loving.</td>
</tr>
<tr>
<td>Phlegm</td>
<td>Phlegmatic</td>
<td>Water</td>
<td>white</td>
<td>salty</td>
<td>Lazy, slow, cowardly, patient, docile,</td>
</tr>
</tbody>
</table>
The gyrating chair was introduced to the USA by Benjamin Rush (1746-1813). It was thought to increase blood supply to the brain. Rush, considered the father of American Psychiatry believed that insanity could be cured by bleeding and purging. The use of leeches in medicine is called Hirudotherapy.
The goals of hydrotherapy were to improve both circulation and the “quality” of the blood. According to Hippocrates, water therapy “allays lassitude” (physical or mental weakness).
Early History of Electrical Stimulation

- The ancient Egyptians used electric catfish out of the Nile to stimulate themselves to treat certain nervous diseases.

- The Roman physician Scribonius Largus treated a patient with gout by using a live torpedo fish. He wrote that headaches and other pains could be cured by standing in shallow water near these electric fish in 46 AD.

- Ibn Sidah was a Muslim doctor of the eleventh century. He believed that a live electric catfish had beneficial effects when placed on the brow of a person suffering an epileptic seizure. The recipes for the torpedo and its ilk have been cited until the end of the renaissance.

The electric catfish has the ability to produce an electric shock of up to 350 volts sing electroplaques of an electric organ.
The Modern History of Electroshock Therapy: Mix and Match of Dates

ECT (1930s)
Induction of a seizure by administration of an electric current to the brain via electrodes placed on the scalp. The exact mechanism of action is unknown, but theories include correction of depletion of inhibitory neurotransmitters, and induction of neurogenesis, particularly in the hippocampus.

TMS (1990s)
Use of a time-variable, intense (-2T), focused magnetic field to induce an electrical field in superficial regions of the cortex. Magnetic field induction causes depolarization or firing of nerve cells in the brain. If repetitive trains of pulses are applied, the repeated firing of neurons over time seems to change their activity.

DBS (2005)
Direct implantation of electrodes into localized brain regions with the aim of altering both local and connected brain activity via ongoing, generally high-frequency stimulation. Electrodes are connected to a pacemaker implanted under the skin on the chest.

EpicS (2007)
A direct cortical stimulation technique that uses implanted electrodes placed above the dura at the desired brain region. Underlying neurons are activated through induction of an electrical field.

100Hz MST (2009)
Induction of a focal seizure via high-frequency repetitive TMS. The seizure originates in the superficial regions of the cortex and, unlike in ECT, no electric current passes through the deeper regions of the brain. The mechanisms of action are as yet unknown.
Changing the excitatory/inhibitory balance of the cerebral cortex can induce cognitive and social impairments in mice which are reversed upon restoring balance (Yizhar et al., Neocortical excitation/inhibition balance in information processing and social dysfunction. Nature, 2011)
tDCS

BBC: “Human enhancement comes a step closer.”

The Star: “Low-level electrical stimulation may make you smarter”.


National Post: “Do-it-yourself brain stimulation has scientists worried as healthy people try to make their minds work better”
The relative cheapness and portability of tDCS means its use is not restricted to laboratories or clinics.
tDCS

Transcranial direct current stimulator

***tDCS v 1.01 (1mA anodal L-DLPFC)***

**Cathode**
- 4.4 x 5 cm
- 25 cm²
- 25.6 m²/cm²
- Place: above right eyebrow
- right supraorbital area

**Anode**
- 5 x 2.4 cm
- 3 x 18.1 cm²
- 55.2 m²/cm²
- Place: L-DLPFC

**Current regulator**
- Front View
- LM317

**Electrodes construction**

**Hoodband construction**

**Battery test**

**9-volt operation**
Modeling the action of tDCS has not taken into account the fact that the human brain provides multiple avenues to crisscrossing conductors (axons) nor the marked convolutions of its surface.
Claims Attributed to tDCS

- Improvements in:

Perception, reasoning, reading, numerical skills, addictive behaviors (smoking), decision making, depression, creativity, memory, schizophrenia (positive symptoms), motivation, migraine, visuomotor skills, epilepsy, aphasia, dystonia, stroke, multiple sclerosis, chronic pain, fibromyalgia, TBI rehabilitation, tinnitus, craving (obesity)
We feel that tDCS is a useful therapeutic intervention particularly for children that have autism with language difficulties. To date, there have been no effective treatment modalities to restore language in minimally verbal children. In combination with functional MRI investigational research being completed at our facility in New York City (Columbia University Program for Imaging and Cognitive Sciences (Schneider, H, 2010)), which demonstrated which brain areas and connections do not function adequately for language, we feel that neuromodulation of these dysfunctional language brain areas will be very successful in combating these language deficits.
Commercial tDCS: Neuroethical Issues

There are no licensing programs. Once bought the machine can be used by anyone (IRB: Justice).
Commercial tDCS: Neuroethical Issues

What is the effect of brain stimulation on the developing brain? Does enhancement of some abilities occurs at the expense of others?

tDCS now targets enhancing learning and cognition in children with typical and atypical development/behaviors. There is a potential for exploitation of vulnerable parents for financial gain.
The Future of tDCS
Repetitive Transcranial Magnetic Stimulation (rTMS)

- Faraday’s Law of Electromagnetic Induction (1831): describes the process by which electrical energy is converted into magnetic fields.

- The TMS apparatus: a power supply discharges current through the TMS coil and this creates a magnetic field pulse (George & Belmaker, 2007).

- The Magnetic Field generated is in the range of 1 tesla (T) (George & Belmaker, 2007; Roth et al., 1991).
TMS Circuitry
Side Effects of TMS

Sometimes a person may have discomfort at the site on the head where the magnet is placed. The muscles of the scalp, jaw or face may contract or tingle during the procedure. Mild headache or brief lightheadedness may result. It is also possible that the procedure could cause a seizure, although documented incidences of this are uncommon. A recent large-scale study on the safety of rTMS found that most side effects, such as headaches or scalp discomfort, were mild or moderate, and no seizures occurred. Long-term side effects are unknown.
Parameters of Stimulation

- 0.5-1 Hz
- 90% of motor threshold (MT)
- Once per week (or 2/week)
- 150-300 pulses per day (10 trains / 15-20 stimuli per train).
- 12 Sessions (6 Left DLPFC, 6 Right DLPFC)
- Currently run 18 sessions
Abnormalities of cortical minicolumnar organization in the prefrontal lobes of autistic patients

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Abstract

Recent functional imaging studies suggest deficits in connectivity between disparate and distant regions in the brains of autistic individuals. One possible explanation to these findings is the presence of modular abnormalities in the neocortex of autistic patients: a change in neuronal specialization within minicolumns that emphasizes short connecting fibers. In this study, we expand on previous findings by exploring the topography of minicolumnar abnormalities in autism. Our postmortem study included six patients with autism (DSM-IV-TR and ADI-R diagnosed) and six age-matched controls. Entire brain hemispheres were celloidin embedded, serially sectioned, and stained with gallocyanin. Digital photomicrographs of n = 9 cortical areas (including paralimbic, heteromodal association, unimodal association, and primary areas) obtained at high magnification were assembled into montages covering the entire cortical thickness. Stained cell somata were segmented from neuropil by thresholding. Computer image analysis clustered neurons into minicolumnar fragments. The full width of the image region nearest each fragment and the width of the cell-dense core of the fragment were estimated. The difference between these two quantities can be used as a measure of the peripheral neuropil space of minicolumns. We found an interaction of diagnosis and region for peripheral neuropil space (p = 0.041). Post hoc analysis revealed significant differences (p < 0.05) for the frontopolar region (area 10) and the anterior cingulate gyrus (area 24). The frontopolar cortex is involved in executive functions by implementing control over internally generated thoughts and relational integration (combination of multiple cognitive rules). The anterior cingulate gyrus is involved in the analysis of socially salient information, including the processing of familiar faces. Pathological findings in these areas may provide a correlate to some of the more salient manifestations of autism.

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Keywords: Minicolumns; Autism; Pervasive developmental disorders of childhood (PDD); Neocortex; Neuropathology; Prefrontal cortex.

I. Introduction

"Indeed, frontal lobe dysfunction may account for much of what makes a person with a mental disorder into a "mental patient" - that is, someone with manifestly abnormal behavior or beliefs." Fogel, pages 8-9, 2001.
Research Design

Overview of the research plan

- Recruitment and screening state
- EEG lab tests
- TMS treatment
- Data analysis

Autism group
- N=38
- Lab visit + Behavioral training visit
- Randomization

Control group
- N=19
- Lab visit
- 3-4 weeks

Psychometric scoring
- EEG data
- ERP data
- ABC, SRS
- RBS, CGI
- ANOVA
- Post-hoc t-tests
- Correlation
- ERP sources
- EEG coherence
- Interpretations

Post-TMS EEG/ERP lab tests
- LF rTMS N=19
- Waiting list N=19

TMS visits
- Total 12 rTMS once/week
- 2-3 months break + 3 rTMS
- Lab visit
- After 6 TMS 9 TMS 12 TMS Follow-up
- Waiting list subjects tested twice

Second EEG/ERP lab tests
- Lab visit
Changes after rTMS

Before rTMS participants with ASD showed large responses over the frontal cortices to all three stimuli with evidence of a lack of stimulus differentiation.
Participants with ASD also showed evidence of a lack of stimulus discrimination compared to controls evidenced by gamma EEG power.
After rTMS individuals with ASD showed significant improvement in cortical discrimination of stimuli as evidenced by gamma EEG power.
Scalp coherence in gamma range post rTMS in autism
Allan Snyder, Ph.D. and Creativity

The controversial professor

Insight Down Under
By JEFFREY FRANCIS

Uludah Mosque | was sold for RM100,000 to an anonymous bidder at an auction of the RDA Charity Ball in aid of the Riding for the Disabled Association in 2004.

Ping Lian’s impressive artworks have been highly praised by American psychiatrist Dr. Darold Treffert as “demonstrating a remarkable ability in an 11-year-old boy whose skills are a striking contrast to limitations in autism and other disabilities”.

This is especially true because autistic savants are supposedly people whose intelligence is considered very limited. Yet they are able to come up with remarkable skills that surprise many talented ordinary people.

Snyder, however, believes that everyone can develop these “islands of genius” by training predictions about the world and devise rules about how to act appropriately.”

Interestingly, an autistic savant can develop mental skill not through training or obsessive practice but from somewhere in his mind. Many of them have suffered brain damage, especially on the left side of the head, after an accident.

Interestingly, too, most of the world’s greatest contributors never had the schooling that is available today. Many of them, including Steve Jobs, the creative genius behind Apple computers, were school dropouts.

In his address to the Canberra school, Snyder calls on everyone not to stick their head in the sand and ignore the fact that only a few have made it to greatness. “Let’s confront it head-on, he urges. “Let’s turn it to our advantage. Let’s begin right here, right now.”

But, ironically, he points out that extraordinarily successful people have never been driven to succeed. They are driven to do something different because of the world that we are unique, that our ways of thinking are different from everyone else, and

Before TMS

After 10 minutes of TMS

After 15 minutes of TMS

...
Violet-Ray Lamp

Looks like a ticklish operation; the treatment, however, is ultra-violet rays.

SUNBURNED backs, as all know, may now be had from a “health lamp”; but here we have a mercury-vapor lamp in a quartz rod, small enough to pass up the nose and sunburn its inside. Four out of five cases of “hay fever” are cured.
Vagus Nerve Stimulation

The vagus nerve stimulator

Doctors at Vanderbilt University Medical Center are treating chronic depression with a device much like a pacemaker that sends impulses to the brain. This new option is for severely depressed people for whom other therapies don’t work.

WHAT IS THE VAGUS NERVE?
One of the primary communication pathways from the major organs of the body to the brain.

HOW THE STIMULATOR WORKS
1. Electrical pulses are created by a generator implanted in the chest.
2. Pulses travel through wires that are attached to the vagus nerve in the neck.
3. Electrodes emitted from the device stimulate the nerve, causing the brain to increase the levels of serotonin and dopamine. These are chemicals in the brain that are believed to affect mood.

SOURCE: Cyberonics, Inc.
KENT RAE / STAFF
Does VNS Work?

- About 30-50% of children gain a significant improvement in seizure control, with reduced seizure frequency or severity.
- Less than 10% of children become seizure free and most continue taking antiepileptic medication.
- Results are similar across all seizure types and syndromes, although there is some suggestion that children with Lennox-Gastaut syndrome and other severe epilepsies may respond better (including Dravet and West syndrome!!!!, see Cerosimo et al. Epileptic Disord 13(4):382-8, 2011).
- Children with recurrent bouts of seizures that escalate to hospitalization often benefit from VNS.
- Termination of prolonged seizures or seizure clusters is possible in some children.
- Currently there is no way to predict response to VNS.
- Many children have improvements in mood, alertness and overall quality of life, even in the absence of significant seizure improvement.
- Seizure reduction is often not evident for several months.
- Over time there may be a continued decline in seizures in many patients. 25% may have a reduction in seizure frequency at 3 months, increasing to 50% after 2 years.
- Results have been mixed when treating Major Depressive Disorder.
Side Effects of VNS

- The most common side effects reported with VNS are hoarse voice, pain or tingling in the throat or neck, cough, headache and ear pain. These effects are generally related to stimulation settings and settle over time or after reduction of stimulation settings.

- Less common side effects of VNS are difficulty sleeping, weight loss, shortness of breath, reduced exercise tolerance, snoring and apnea during sleep, vomiting, facial flushing, dizziness and irritability.

- Swallowing problems and rarely aspiration may occur in some children with disabilities, feeding difficulties and reflux.

- Wound breakdown, wound infection and device damage are rare but potentially serious complications.

- Cessation of heart beat has been rarely reported in adults undergoing VNS implantation, during the intraoperative lead test, but this has not been reported in children.
Precautions with VNS

- Physical trauma to the pulse generator or lead wire, such as with rough sport or neck manipulation, can damage the device.

- Equipment that may interfere with the stimulator should be avoided. These include strong magnets, hair clippers and loudspeakers. Some medical tests, such as MRI scans, can interfere with the device. Always tell health professionals that your child has a VNS implanted.

- The neurologist or epilepsy nurse specialist should always be consulted prior to any medical imaging, diagnostic testing or surgical procedures, to ensure patient safety and device integrity. The pulse generator may need to be turned off temporarily and special precautions may need to be taken with anesthesia, surgery or scanning.

- Always avoid areas where pacemaker warning signs are posted.

- The magnet provided for manual stimulation may damage credit cards, mobile phones, computer disks, televisions and other items affected by strong magnetic fields. Care should be taken to store magnet away from these types of equipment.
Deep Brain Stimulation (DBS)

DBS does not create a lesion in the target area and stimulation can be adjusted. The pacemaker battery needs to be replaced, when necessary, under anesthetic. The procedure is extremely expensive and only available in certain centers.
DBS: Targeted Site

Indications: dystonia, tremor, epilepsy, obsessive compulsive disorder, pain, depression
DBS: Does It Work?

- Provides moderate relief for approximately 90% of patients with essential tremor.

- In Parkinson’s disease, over 70% experience a significant improvement in all of their symptoms and a reduction in terms of medication usage. Similar improvements have been noted in cervical dystonia.

- How do you keep a trial blinded, what are the sham controls?
Deep Brain Stimulation Risks

- **Surgery and Post Surgery:**
  
  Bleeding in the brain, stroke, infection, breathing problems, nausea, heart problems, seizures, hardware complications (e.g., corroded lead wire)

- **Side effects of Stimulation:**

  Numbness or tingling sensation, muscle tightness, speech problems, balance problems, lightheadedness, unwanted mood changes
of certain highly contagious and infectious diseases, can be traced to faulty circulation and impure blood.”
(http://www.electroherbalism.com/Bioelectronics/Tesla/VioletRay.htm)

- The first prototype introduced by Tesla in 1893. Tens of thousands were sold for home use from 1915 to 1950.

- Said to cure everything, e.g., lumbago, wry neck, heart disease, carbuncles, writers cramp.

- Still today the Violet Wand used as a sexual stimulation device and the High Frequency Aesthetic Device used to oxygenate the skin. (Low current, high voltage and high frequency)
## SAFETY CONCERNS

<table>
<thead>
<tr>
<th>Current level in milliamperes</th>
<th>Probable effect on the human body</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mA</td>
<td>Tingling sensations and a change in perception levels.</td>
</tr>
<tr>
<td>5 mA</td>
<td>A subtle shock. The individual is able to let go of the object. Intense involuntary spasms might lead to injury.</td>
</tr>
<tr>
<td>6-16 mA</td>
<td>A painful shock. Loss of muscular control. Often referred to as a freezing current where the individual cannot separate from the electrical source.</td>
</tr>
<tr>
<td>17-99 mA</td>
<td>Extreme pain, lung failure, strong muscular contractions. Inability to separate from electrical source. Possibly fatal.</td>
</tr>
<tr>
<td>100-2000 mA</td>
<td>Severely abnormal heartbeat. Extreme muscular contractions and nerve damage occur. Likely resulting in death.</td>
</tr>
<tr>
<td>&gt;2,000 mA</td>
<td>Heart stops beating, internal organs are severely damaged and extreme burns. Probable death.</td>
</tr>
</tbody>
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![Diagram of electrical safety concerns](image-url)
Electroconvulsive Therapy

- The story of electroconvulsive therapy (ECT) began in 1938, when Italian psychiatrist Ugo Cerletti visited a Rome slaughterhouse to see what could be learned from the method that was employed to butcher hogs.

- In Cerletti’s own words, “As soon as the hogs were clamped by the [electric] tongs, they fell unconscious, stiffened, then after a few seconds they were shaken by convulsions....

- During this period of unconsciousness (epileptic coma), the butcher stabbed and bled the animals without difficulty....

- “At this point I felt we could venture to experiment on man, and I instructed my assistants to be on the alert for the selection of a suitable subject.” Cerletti’s first victim was provided by the local police - a diagnosed schizophrenic with delusions, hallucinations and confusion.

- After surviving the first blast without losing consciousness, the victim overheard Cerletti discussing a second application with a higher voltage. He begged Cerletti, “Non una seconda! Mortifiere! (“Not another one! It will kill me!”) Ignoring the objections of his assistants, Cerletti increased the voltage and duration and fired again. With the ‘successful’ electrically induced convulsion of his victim, Ugo Cerletti brought about the application of hog-slaughtering skills to humans.

Cerletti received a honorary degree by the Sorbonne (University of Paris) and a long list of awards.
ECT

- Most individuals that respond do so within 3 to 4 treatments. Usually treatments are extended for 10-12 sessions given during a period of 2-3 weeks (2 to 3 times per week). (Note: TMS requires some 30 sessions at about $250 per session)

- Bitemporal application is the most effective method but also the one with most side effects.

- There are no absolute contraindications to ECT. It has been proven safe in elderly regardless of age, pregnant women and children. Good for psychotic subtype, catatonia, higher baseline HRSD, and older age (all predictors of poor response to TMS)
Electroconvulsive Therapy

No other treatment ever been shown to be more effective in the acute treatment of Major Depression. Best when depression has lasted less than 2 years and there are no other psychiatric disorders.

We really do not understand how ECT works in treating, among others, depression, schizophrenia, bipolar disorder and catatonia.

1) One explanation is that the electric shock increases the levels of serotonin and norepinephrine.

2) ECT may also increase neurogenesis (in rats).
ECT Side Effects

Most common side effects are headaches, upset stomach, muscle aches, and memory problems, especially for memories around the time of the treatment. In the past, before muscle relaxants and sedation, there were also bone fractures.