Clinical Applications of tDCS: past, present and future

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Is there an unmet clinical need for development of tDCS as a clinical tool?

- Current treatments
- Brain plasticity
- Development of novel markers
Failure of current pharmacological treatments for chronic diseases in neurology, psychiatry and rehabilitation

• Main principle of pharmacological treatment may lead to detrimental long-term effects – concept of dynamic effect

• Example of aberrant plasticity in Parkinson’s disease and chronic pain
Role of neuroplasticity: example of failure of dopaminergic drugs

Adaptive Learning

Non-adaptive Learning

Zhuang 2013
Another example:

*Aberrant plasticity in chronic pain: does analgesic drug enhance aberrant plasticity?*

Drugs can enhance learning of anticipation of pain and modulation of perception circuits

Apkarian, 2013
Therapeutic effects of noninvasive brain stimulation

- Duration of effects ("repair" vs. "interaction" model – Ridding, 2007)
  - Repair model – corrects an imbalance in function (for example – Levodopa for PD)
  - Interaction model – help the brain to restore itself – promotion of plasticity
Neural guided application of tDCS

• Functional plasticity is accompanied by structural plasticity.
• Functional plasticity in intact cortex begins immediately after injury.
• Neurosciences and clinical sciences should be coupled for therapeutic purposes.
Basic Idea of Neuromodulation
Basic Idea of Neuromodulation
Basic Idea of Neuromodulation

=
Activity/stimulation vs. Chemical Activation

Chemical – ON/OFF – maladaptive learning
Activity/stimulation – long-lasting changes
How about combination??
Rationale for Electrotherapy

• Broad spectrum (*neuropsychiatry, neuropsychology, rehabilitation, cognitive performance...*)
• Individualized therapy
• Targeted brain modulation (*space + time*)
• Adverse effects (*minimal complications + counter-indications*)
• Mechanism of actions vs. mechanisms of disease
• Cost
What is different now?

• Knowledge on mechanisms of neuroplasticity – in healthy and disease

• Better control and focality of stimulation
What are the options?

Different electrodes/coils

Transcranial Electrical

Transcranial Magnetic

Invasive Leads
(also Vagus, Spinal..)

Figure from Marom Bikson
Transcranial Direct Current Stimulation (tDCS)

- Optimal tool to modulate practice-related learning neural activation.
- Changes in network associated with practice.
- Enhancement might be useful for initial stages of learning during skill acquisition and at later stages for learning consolidation.
- Combined therapy with pharmacological, physical, and cognitive/behavioral approaches.
Future devices?

• Better TENS stimulation devices?

• Other non-invasive cranial nerve stimulation devices?

• Using other forms of neural stimulation alone or in combination: mechanical, thermal
Past and Present: what have we learned in the past 30 years of research with tDCS
17 years of tDCS….or 50 years of brain polarization?

- Parameters of stimulation
- Safety protocols
- Clinical Trials
- Combined protocols
What did we learn regarding parameters of stimulation?

Main effects will depend not only of parameters of stimulation but combination parameters + ongoing neural activity.
Parameters of Stimulation - tDCS

- Anodal vs. cathodal effect
- Anodal: depolarization  Cathodal: hyperpolarization
- Effects may depend on task and baseline cortical activity

Nitsche et al, 2000

Fregni et al, 2006
Location of stimulation - tDCS

- Reference electrode has a critical impact
- Different strategies: 1x1; 1x0; 2x1; 4x1

Mendonça et al, 2011

Nitsche et al, 2011
Safety – tDCS I

- Animal study – Liebetanz et al, 2009
Safety – tDQS II

Transcranial direct current stimulation in patients with skull defects and skull plates: High-resolution computational FEM study of factors altering cortical current flow

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Datta et al., 2010
Safety of tDCS III

• Brunoni et al., 2011 – Systematically reviewed reports of AE’s in human studies of patients and healthy subjects.
  – 172 articles (209 studies) included
  – 117 studies assessed AE’s
  – 74 studies reported at least 1 AE

• Findings for Active Stimulation:
  – Most commonly reported effects are mild
  – Itching (39.3%)
  – Tingling (22.2%)
  – Headache (14.8%)
  – Burning sensation (8.7%)
  – Discomfort (10.4%)
Efficacy/clinical effects - tDCS

- Several small studies have shown tDCS is efficacious

- But effects sizes are small in some of these studies or heterogeneity is large across studies
Problem of small studies

Figure 5  Funnel plot (publication bias assessment) of the effect sizes (Cohen d) according to their standard errors. The horizontal solid line is drawn at the pooled effect size, and angled lines represent the expected 95% confidence interval for a given standard error, assuming no between study heterogeneity.
Meta-analysis

• Tinnitus meta-analysis: 17 identified only 2 RCTs were included. Overall 39.5% responded to active tDCS with a mean tinnitus intensity reduction of 13.5%. **Not enough studies – Song et al, 2012**

• Chronic stroke meta-analysis: 8 studies - pooled analysis showed a significant increase in scores in favor of tDCS compared to sham (SMD=0.49, 95% CI=0.18-0.81, p=0.005) – small effect size - Butler et al, 2013

• Major depression meta-analysis: 6 studies - active tDCS was found to be more effective than sham tDCS for the reduction of depression severity (Hedges' g=0.743, 95% confidence interval 0.21-1.27) - results differed more than expected by chance (Q=15.52, df=6, p=0.017, I²=61.35) – significant heterogeneity - Kalu et al., 2012
Methods of focalizing/enhancing the effects of NIBS

- Combination protocols
- Optimal dosages
Effectiveness of transcranial direct current stimulation and visual illusion on neuropathic pain in spinal cord injury

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Combination protocols - stroke

Neurophysiological and Behavioral Effects of tDCS Combined With Constraint-Induced Movement Therapy in Poststroke Patients

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- Increasing activity in the affected M1 by Anodal tDCS and motor training of affected hand
- Decreasing activity in the healthy M1 by Cathodal tDCS and unaffected arm restriction

(A) (B)

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure.png}
\caption{A comparison of JHFT scores between Active tDCS and Sham tDCS over different time points.}
\end{figure}
Combination protocols – major depression

The Sertraline vs Electrical Current Therapy for Treating Depression Clinical Study

Results From a Factorial, Randomized, Controlled Trial

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Importance: Transcranial direct current stimulation (tDCS) trials for major depressive disorder (MDD) have shown positive but mixed results.

Objective: To assess the combined safety and efficacy of tDCS vs a common pharmacological treatment (sertraline hydrochloride, 50 mg/d).

Design: Double-blind, controlled trial. Participants were randomized using a 2 × 2 factorial design to sertraline/placebo and active/placebo tDCS.

Setting: Outpatient, single-center academic setting in São Paulo, Brazil.

Participants: One hundred twenty antidepressant-free patients with moderate to severe, nonpsychotic, unipolar MDD.

Intervention: Six-week treatment of 2 mA anodal left/medial right prefrontal tDCS (twelve 30-minute sessions; 10 consecutive sessions once daily from Monday to Friday plus 2 extra sessions every other week) and sertraline hydrochloride (50 mg/d).

Main Outcome Measures: In this intention-to-treat analysis, the primary outcome measure was the change in Montgomery-Asberg Depression Rating Scale score at 8 weeks (end point). We considered a difference of at least 3 points to be clinically relevant. The analysis plan was previously published. Safety was measured with an adverse effects questionnaire, the Young Mania Rating Scale, and cognitive assessment. Secondary measures were rates of clinical response and remission and scores on other scales.

Results: At the main end point, there was a significant difference in Montgomery-Asberg Depression Rating Scale scores when comparing the combined treatment group (sertraline + active tDCS) vs sertraline only (mean difference, 8.85 points; 95% CI, 2.96 to 14.70; P = .002), tDCS only (mean difference, 5.9 points; 95% CI, 0.35 to 11.43; P = .031), and placebo + sham tDCS (mean difference, 11.3 points; 95% CI, 6.03 to 17.10; P < .001). Analysis of tDCS only vs sertraline only presented comparable efficacies (mean difference, 2.6 points; 95% CI, −2.90 to 8.13; P = .33). Use of tDCS only (but not sertraline only) was superior to placebo + sham tDCS. Common adverse effects did not differ between interventions, except for skin redness on the scalp in active tDCS (P = .03). There were 7 episodes of treatment-emergent manic or hypomanic, 5 occurring in the combined treatment group.

Conclusions and Relevance: In MDD, the combination of tDCS and sertraline increases the efficacy of each treatment. The efficacy and safety of tDCS and sertraline did not differ.

Trial Registration: clinicaltrials.gov Identifier: NCT01035106

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Future of Non-invasive Brain Stimulation: 
given what we have learned what is next?
Areas of Investigation

- Chronic use
- Safety
- Portability
- Automatic detection and regulation of stimulation: developing novel markers
- Novel and modified devices
Novel methods to optimize the effects of transcranial direct current stimulation: a systematic review of transcranial direct current stimulation patents

Transcranial direct current stimulation (tDCS) is a neuromodulatory technique that has been extensively studied. While there have been initial positive results in some clinical trials, there is still variability in tDCS results. The aim of this article is to review and discuss patents assessing novel methods to optimize the use of tDCS. A systematic review was performed using Google patents database with tDCS as the main technique, with patents filling date between 2010 and 2015. Twenty-two patents met our inclusion criteria. These patents attempt to address current tDCS limitations. Only a few of them have been investigated in clinical trials (i.e., high-definition tDCS), and indeed most of them have not been tested before in human trials. Further clinical testing is required to assess which patents are more likely to optimize the effects of tDCS. We discuss the potential optimization of tDCS based on these patents and the current experience with standard tDCS.
Developing closed loop systems (real-time monitoring/stimulation) – combination with metacognitive strategies

• Challenge: finding good markers of response
Developing Novel Markers: Markers for chronic pain

• Neuroimaging

Wager et al, 2013
Intracortical inhibition/TMS cortical excitability

Primary motor cortex plasticity in osteoarthritis chronic pain

Maria da Graça Tarrago, Liciane F Medeiros, Iraci L. S. Torres, Liliane P Vidor, Alicia Deitos, Aline Brietzke, Felipe Fregni, Wolnei Caumo
Or Quantitative EEG/ERP?
Our Fibromyalgia trial

To find the optimal protocol for FM (optimal dosage) and preliminary assessment of ERP as a response marker

Collaborative Team:
Spaulding/Harvard: Laura Castillo, Rivail Brandao, Nigel Geboth, Livia Coutinho, Sarah Daly
CUNY/CCNY: Marom Bikson
Basic protocol
Pre-Screening
via phone, to determine eligibility
Target Enrollment: 15 Patients

Visit 1
Baseline Assessments and EEG/CHEPS
One week before stimulation

Visits 2-11 Stimulation

Non-responders continue

Visits 12-21 Stimulation

Non-responders continue

Visits 22-27 Stimulation

Follow up Visits
(2 weeks and 8 weeks post Stimulation)

Visits 2, 5, 8, 11: 2x EEG/CHEPS
Visits 6, 11: Assessments

Visits 16 and 21: Assessments

Visits 24 and 27: Assessments
Preliminary results - Behavioral

The graph shows VAS Reports Over Time, with days in trail on the x-axis and VAS report (0-10) on the y-axis. The data fluctuates over the course of the trail, with some notable peaks and troughs.
Averaged CHEPS VAS Ratings for Low High Temp Pre and Post tDCS

- **Visit 2**: Pre tDCS Low Temp (1.5) and Post tDCS High Temp (3.5)
- **Visit 6**: Pre tDCS Low Temp (1.5) and Pre tDCS High Temp (3.0)
- **Visit 7**: Pre tDCS Low Temp (1.5) and Post tDCS Low Temp (1.0)
- **Visit 11**: Post tDCS Low Temp (1.0) and Post tDCS High Temp (2.0)
ERP – Baseline – N2/P2

Low Temp Stim
High Temp Stim
ERP after 11 days
Other markers: real-time FFT EEG analysis

Effects of non-pharmacological pain treatments on brain states

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Fig. 1. Pre- to post-session changes in absolute bandwidth at different electrode sites.
Portable EEG devices/stimulation devices
Conclusions

• There has been an intense development and interest in tDCS
• Results are encouraging, but protocols need to be optimized
• Use of protocols to enhance plasticity combined with real-time monitoring will likely lead to optimal results
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