Non-invasive neuromodulation in the post COVID-19 world

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Disclosure
The City University of New York: Patents on brain stimulation.
Soterix Medical: Produces tDCS and High-Definition tDCS.
Boston Scientific: Neuromodulation Scientific Advisory Board
GlaxoSmithKline (GSK): Life Science Scientific Advisory Board
Mecta, Biovisics, Humm, Halo Neuroscience, Google X, i-Lumen,
Biovisics, Apple

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Harold Shames, CCNY Fund, 21st Century Fund, “X”
Neuromodulation technologies platforms vary in how energy is delivered to what target:

- Deep Brain Stimulation (DBS)
- Spinal Cord Stimulation (SCS)
- Transcranial Magnetic Stimulation (TMS)
- Electroconvulsive Therapy
- Transcranial Electrical Stimulation (tES)
- Transcranial Direct Current Stimulation (tDCS)
Neuromodulation technologies platforms vary in how energy is delivered to what target:

- **Implants**
  - Deep Brain Stimulation (DBS)
  - Spinal Cord Stimulation (SCS)

- **In-Hospital**
  - Transcranial Magnetic Stimulation (TMS)
  - Electroconvulsive Therapy

- **Wearable**
  - Transcranial Electrical Stimulation (tES)
  - Transcranial Direct Current Stimulation (tDCS)

**COVID-19:** Low risk. Allows home-based or low-cost, portable in-hospital therapy.
Applications of Non-invasive Neuromodulation for the Management of Disorders Related to COVID-19

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1) Neuromodulation targets etiology of COVID-19.
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Pick the right neuromodulation technique based on mechanism of action (hypothesis).
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Decades of trials in non-COVID-19 populations.

**Acute**

- **A)** Direct infection mitigation through the stimulation of regions involved in the regulation of systemic anti-inflammatory responses and/or autonomic responses.

- **B)** Amelioration of COVID-19 symptoms of musculoskeletal pain and systemic fatigue.

**Post-Acute**

- **C)** Outbreak-related mental distress including neurological and psychiatric disorders exacerbated by psychosocial stressors related to COVID-19.

- **D)** Augmenting cognitive and physical rehabilitation following critical illness.

- **X)** Long-COVID, Neuro-COVID, Post-Acute Sequelae of SARS-CoV-2 infection (PASC)

Decades of trials in non-COVID-19 populations. Ongoing trials.

C) Outbreak-related mental distress including neurological and psychiatric disorders exacerbated by psychosocial stressors related to COVID-19.

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Guidelines for TMS/tES clinical services and research through the COVID-19 pandemic

Marom Bikson a, Colleen A. Hanlon b, Adam J. Woods c, Bernadette T. Gillick d, Leigh Charvet e, Claus Lamm f, Graziella Madeo g, Adrienn Holczer h, Jorge Almeida i,j, Andrea Antal k,l, Mohammad Reza Ay m, Chris Baeken n.o.p, Daniel M. Blumberger q.r, Salvatore Campannela s, Joan A. Camprodon t, Lasse Christiansen u, Colleen Loo v, Jennifer T. Crinion w, Paul Fitzgerald x, Luigi Gallimberti g, Peyman Ghobadi-Azbari y.z, Iman Ghodratitoostani aa, Roland H. Grabner ab, Gesa Hartwigsen ac, Akimasa Hirata ad, Adam Kirton ae, Helena Knotkova af.ag, Evgeny Krupitsky ah, Paola Marangolo ai.aj, Ester M. Nakamura-Palacios ak, Weronika Potok al, Samir K. Praharaj am, Christian C. Ruff an, Gottfried Schlaug ao, Hartwig R. Siebner u.ap, Charlotte J. Stagg aq, Axel Thielischer u.ar, Nicole Wenderoth al, Ti-Fei Yuan as, Xiaochu Zhang at, Hamed Ekhtiari au.a
Non-invasive Neuromodulation / tDCCS
Going home (in the time of COVID-19)
Transcranial electrical stimulation (transcranial Direct Current Stimulation) and transcutaneous Auricula Vagus Nerve Stimulation (taVNS) 

From in-clinic to “Remote-Supervised” Neuromodulation platform.
Remotely-supervised transcranial direct current stimulation (tDCS) for clinical trials: guidelines for technology and protocols

Leigh E. Charvet¹, Margaret Kasschau¹, Abhishek Datta², Helena Knotkova³, Michael C. Stevens⁴, Angelo Alonzo⁵, Colleen Loo⁵, Kevin R. Kurl⁶ and Marom Bikson⁷

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Expertise of operator

Home-use
Self application or Supervised

Clinic
Trained operator

Medical center or University
Increased automation

**Home:** Fully automatic, No flexibility

**Clinic:** Semi-automatic  Some flexibility

**Medical Center:** Customization, flexibility, integration with other equipment
Is more risk acceptable in any case?

How we remotely regulate stimulation and monitor compliance and outcomes

Manage Risk

Home

Clinic

Medical Center
Biomarkers / Imaging integrated with Neuromodulation (at home)

- Heart rate, blood pressure
- functional Near Infrared Spectroscopy
- Mobile EEG and physiology
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FDA IDE trial: tDCS-LTE for Depression

• Motivated in part by limited access FDA approved in-clinical treatments (rTMS, ECT)

• Home-based transcranial Direct Current Stimulation Limited-Total-Energy platform (TDCS\textsuperscript{LTE})

• Device: Remote control of dosing and compliance monitoring

• Contactless

• First center: New York University, Langone Health

• Mix of automated (ElectraR\textsubscript{x}) symptom monitoring and telemedicine
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To develop effective and personalized PASC treatments: Neuromodulation should be objective biomarker guided (target engagement)

Patient 1: A 42-year-old, right-handed, Black woman presented for tDCS clinical treatment of PASC in 01/2021, approximately nine months following COVID-19 illness. She continued to experience fatigue, cognitive impairment, anxiety and depression, dyspnea, sleep disturbances, and numbness sensation in the right side of her face.

Patient started her tDCS treatment in January 2021. A comparison between initial (08/2020) and repeat (02/2021) neuropsychological evaluations following 4 weeks of treatment (15 sessions) demonstrated significant improvements (≥1 SD) in visual attention and processing speed, timed verbal fluency, and cognitive flexibility. Speeded fine motor dexterity was also improved in her left hand (and remained intact in her right hand). She also reported clinically significant improvements in cognitive functioning, depression, and fatigue. Anxiety ratings increased, indicating ongoing mild anxiety (which she attributed to her approaching return to work). Sleep remained unchanged and within normal limits. The A-PASC inventory indicated significant improvements across all affected domains. Importantly, over the course of treatment, the patient returned to her job, gradually increasing her work responsibilities.

Patient 2: A 57-year-old, right-handed, White woman presented for tDCS clinical treatment of PASC in November 2020, approximately seven months following COVID-19 illness. She experienced a constellation of persisting symptoms, including marked fatigue and “brain fog,” emotional dysregulation, intermittent numbness in her extremities, and pain.
taVNS for “neuro-COVID” (PASC)

• Subjects who are post COVID but experience any lasting (new) neurological or psychiatric symptom. Center: Medical University of South Carolina
• Device: Remote control of dosing and compliance monitoring

• tAVNS dual action: parasympathetic activation + direct brain modulation

• Contactless

• Integrated remote real-time physiology monitoring (HR, oximeter)

• Mix automated (ElectraRx) symptom monitoring and telemedicine
tDCS for Post-Acute Sequelae of SARS-CoV-2 infection (PASC)

• Subjects who are post COVID but experience any lasting (new) neurological or psychiatric symptom. Center: Universidade de São Paulo (USP)

• tDCS + Digital Healthcare

• Physiological biomarkers of symptoms and tDCS symptom response

• At center with home-ready (contactless) platform

Trial ongoing
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HD-tDSC to reduce need for Mechanical ventilation duration (MVD) in ICU

• Covid-19 patients admitted to the Metropolitan Hospital's ICU. Governo do Estado da Paraíba

• 2-4 mA High-Definition tDSC (HD-tDCS) to allow targeting of cortical region (rapid deployment disposable, head-gear version)

• Ventilatory weaning in patients admitted to the Intensive Care Unit (ICU) and to improve the respiratory performance (decreases in mechanical ventilation duration and diaphragmatic impairment).

• Trial completed. Results disclosure pending.
Transcranial Direct Current Stimulation (tDCS) is a wearable brain stimulator applying Direct Current (no pulses) (Probably) most investigated interventional neurotechnology
**tDCS: transcranial Direct Current Stimulation**

- **Anode (+) Electrode**
- **Cathode (-) Electrode**

"Anodal" / "Cathodal" refer to proximity of target

- 2 mA
- 20 minute session
- Mild tingling sensation
- No overt brain response
"Cathodal" tDCS
Soma hyper-polarized
Brain function "dampened"

"Anodal" tDCS
Soma depolarized
Brain function "boosted"

Radman et al. Role of cortical morphology in uniform electric field stimulation. Brain Stim. 2013
For a given head anatomy, a given electrode placement, where in the brain does current go?

Datta et al. Gyri-precise model of tDCS/ Brain Stimulation 2009
M1-SO tDCS

Brain Activation
- Maximum
- Moderate
- Minimum

(Electric Field)

Datta et al. Gyri-precise model of tDCS/ Brain Stimulation 2009
M1-SO tDCS

Datta et al. Gyri-precise model of tDCS/ Brain Stimulation 2009
High-Definition tDCS – 4x1

Brain Activation
- Maximum
- Moderate
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Datta et al. Gyri-precise model of tDCS/ Brain Stimulation 2009
High-Definition tDCS – 4x1

Datta et al. Gyri-precise model of tDCS/ *Brain Stimulation* 2009
It is well established: Direct Current stimulation is a powerful modulatory of ongoing plasticity

Direct current stimulation boosts hebbian plasticity in vitro

Greg Kronberg*, Asif Rahman¹, Mahima Sharma, Marom Bikson, Lucas C. Parra
There is a strong mechanistic and empirical foundation to testing (bio-marker guided) non-invasive brain stimulation treatment for COVID-19, ranging from ICU-based to home-based (PASC) applications.

This work is critical.
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Slides and References @MaromBikson