



National Institutes of Health
Office of Disease Prevention



Office of Disease Prevention
Putting Prevention Research First

Prevention SIG Webinar Series

Welcome! We will begin shortly.



Save The Date!

Wednesday, January 26, 2022, 3:00 PM ET

“Update 2022: COVID-19, Multisystem Inflammatory Syndrome in Children, and the Heart”

Jane W. Newburger, M.D., M.P.H.

Associate Cardiologist-in-Chief for Academic Affairs, Department of Cardiology, Boston Children’s Hospital;
Commonwealth Professor of Pediatrics, Harvard Medical School



Dongngan Truong, M.D., M.S.

Associate Professor of Pediatrics, Division of Pediatric Cardiology, University of Utah and Primary Children’s
Hospital

Introduction by Victoria Pemberton, R.N.C., M.S., C.C.R.C., Program Officer, NHLBI



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“Does Transcranial Direct Current Stimulation Have a Role in the Management of Multiple Sclerosis Symptoms?”



Presented by

[Leigh E. Charvet, Ph.D.](#)

Director of Multiple Sclerosis Research and Professor of Neurology, New York University Langone Health

Introduction by **[Jennifer N. Baumgartner, Ph.D.](#)**, Health Scientist/American Association for the Advancement of Science (AAAS) Science and Technology Policy Fellow, NIH/Office of Disease Prevention



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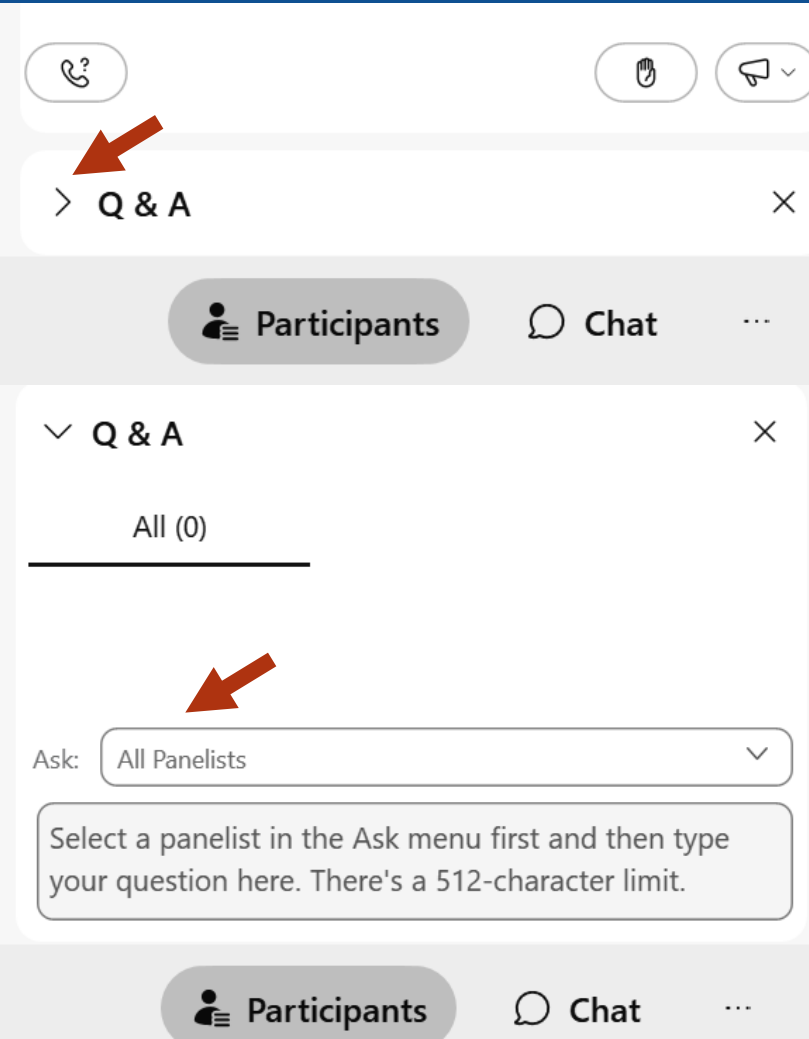
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Upcoming Q & A Session

Please send us your questions via the
Q & A pod directed to All Panelists

You may use the Chat pod for general commentary or to
request technical assistance





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“Does Transcranial Direct Current Stimulation Have a Role in the Management of Multiple Sclerosis Symptoms?”



Presented by

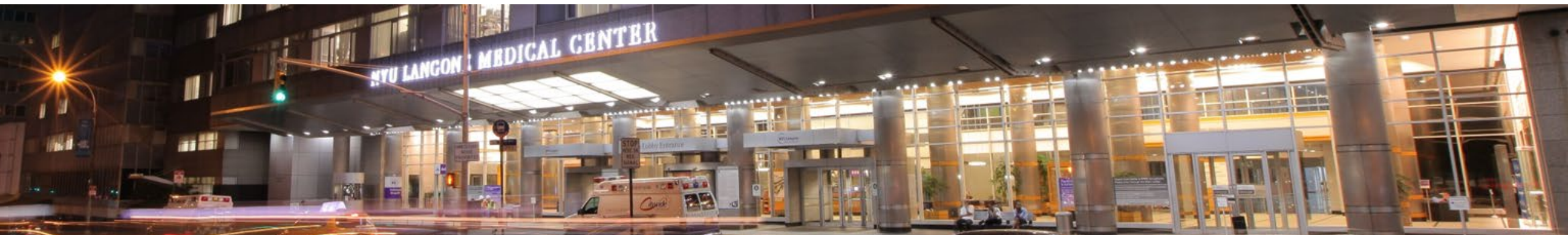
[Leigh E. Charvet, Ph.D.](#)

Director of Multiple Sclerosis Research and Professor of Neurology, New York University Langone Health

Introduction by **[Jennifer N. Baumgartner, Ph.D.](#)**, Health Scientist/American Association for the Advancement of Science (AAAS) Science and Technology Policy Fellow, NIH/Office of Disease Prevention

DOES TRANSCRANIAL DIRECT CURRENT STIMULATION HAVE A ROLE IN THE MANAGEMENT OF MULTIPLE SCLEROSIS SYMPTOMS?

Leigh Charvet PhD
Director of MS Research
Professor of Neurology



- Disclosures:
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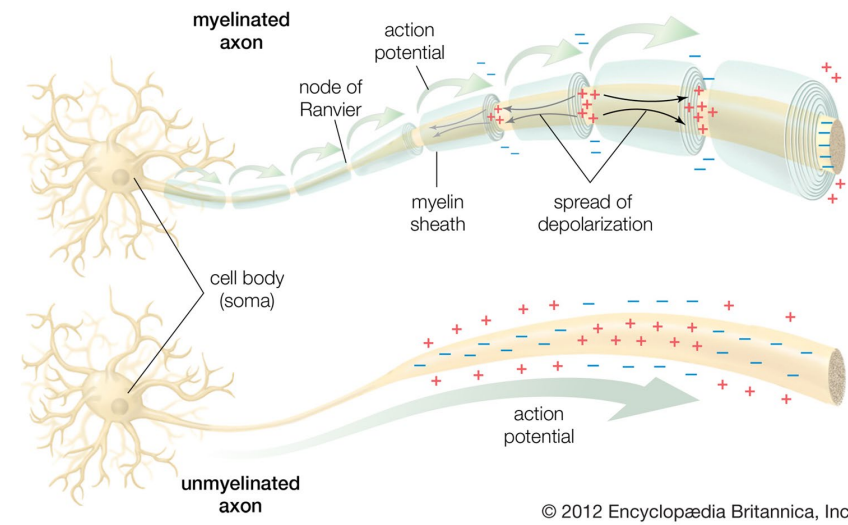
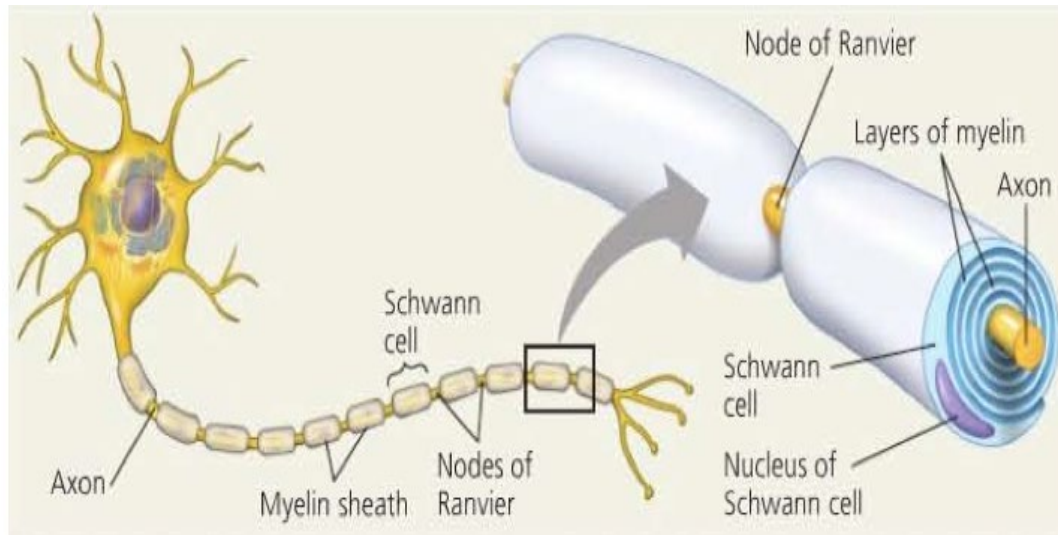
1. Why tDCS? The unmet need of MS symptom burden
2. tDCS overview
3. Our approach with participation from home: Remotely Supervised (RS)-tDCS
4. RS-tDCS studies in MS

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1. **Why tDCS? The unmet need of MS symptom burden**
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MS is a chronic, progressive, and common CNS disease

- >1 million people in the U.S. alone
- 3:1 women to men
- Lifespan disease: typical age of onset in early adulthood (20 to 50 years)
- Progressive and without cure- but does not significantly alter life expectancy



© 2012 Encyclopædia Britannica, Inc.

Progressive Symptom Burden

❖ Relapsing-remitting MS (RRMS)

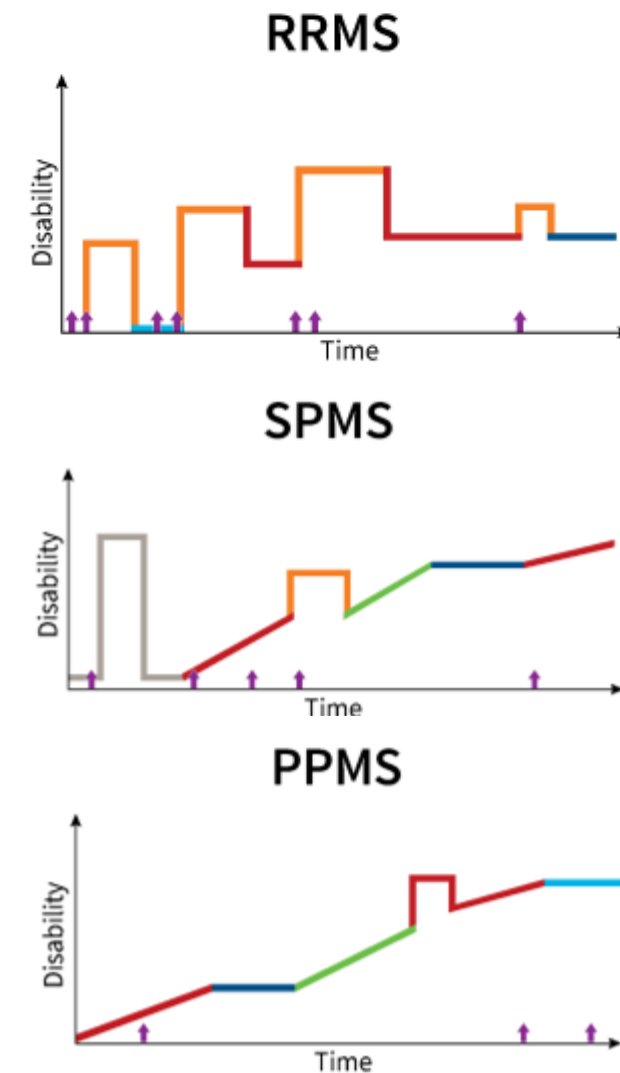
- 80-85% of new onset MS.
- Acute episodes of neural dysfunction followed by recovery to varying extents (no full recovery)
- Accumulated disability over time
- Frequency of relapses can be significantly reduced by disease-modifying treatments (DMTs)

❖ Secondary progressive MS (SPMS)

- Acute episodes are replaced with a slow steady increase in symptom severity.
- Pattern usually changes after 5-25 years post-onset.
- Limited response to immunotherapy.
- High rates of disability
- High rates of cognitive involvement

❖ Primary progressive MS (PPMS)

- Less than 10% of patients.
- Slow steady deterioration without acute episodes.
- Limited response to immunotherapy.
- High rates of disability
- Usually greater involvement of spinal cord; cognition is relatively preserved



(Lublin et al., 2014; Di Filippo et al., 2018)

MS Symptom Burden: Unmet Need

- MS results in cumulative CNS damage over time
- Disease-modifying therapies (DMTs) slow disease activity...but do not directly target MS symptoms
- Increasing symptom burden over disease course...resulting in disability and reduced quality of life
- Goal is for reliable and effective options for symptomatic management

Diverse and varying range of persisting symptoms



Cognitive
Dysfunction

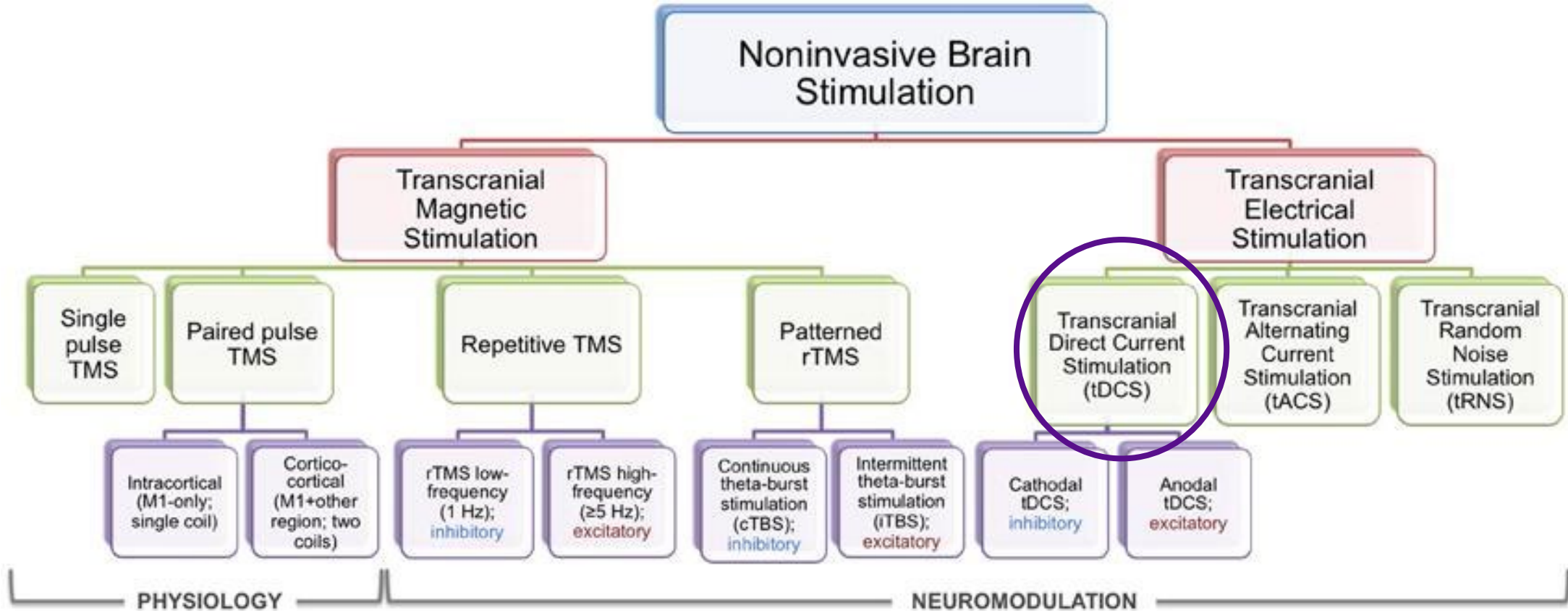
Motor
Dysfunction

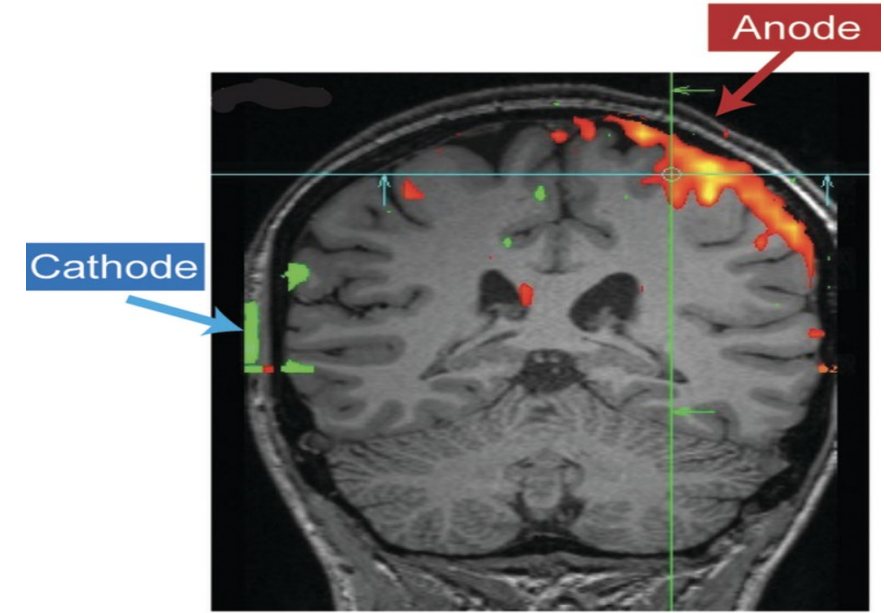
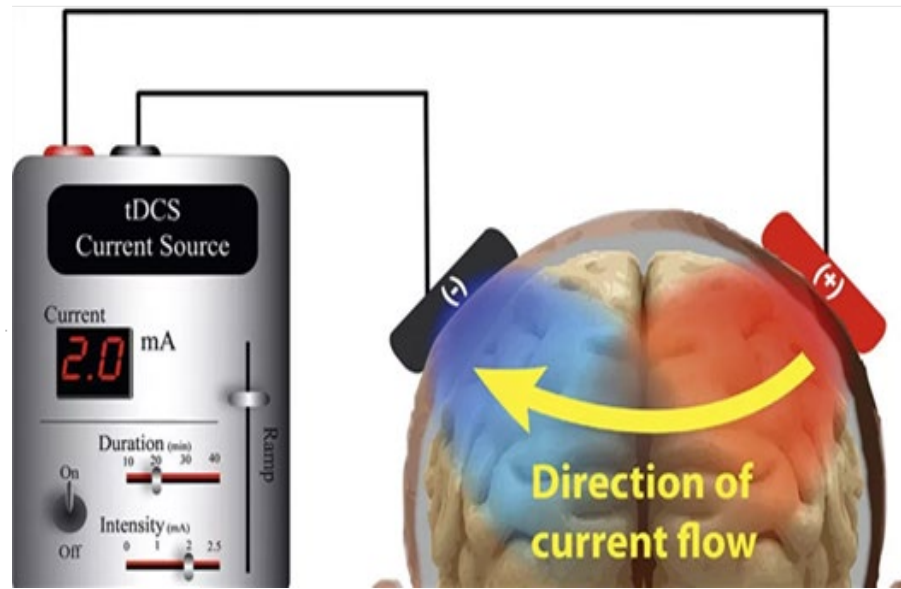
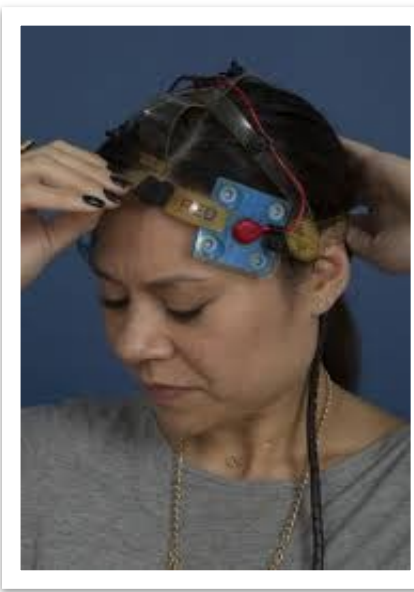
“Invisible
Symptoms”

Fatigue
Distress/Depression
Pain

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4. RS-tDCS studies in MS

Noninvasive Brain Stimulation

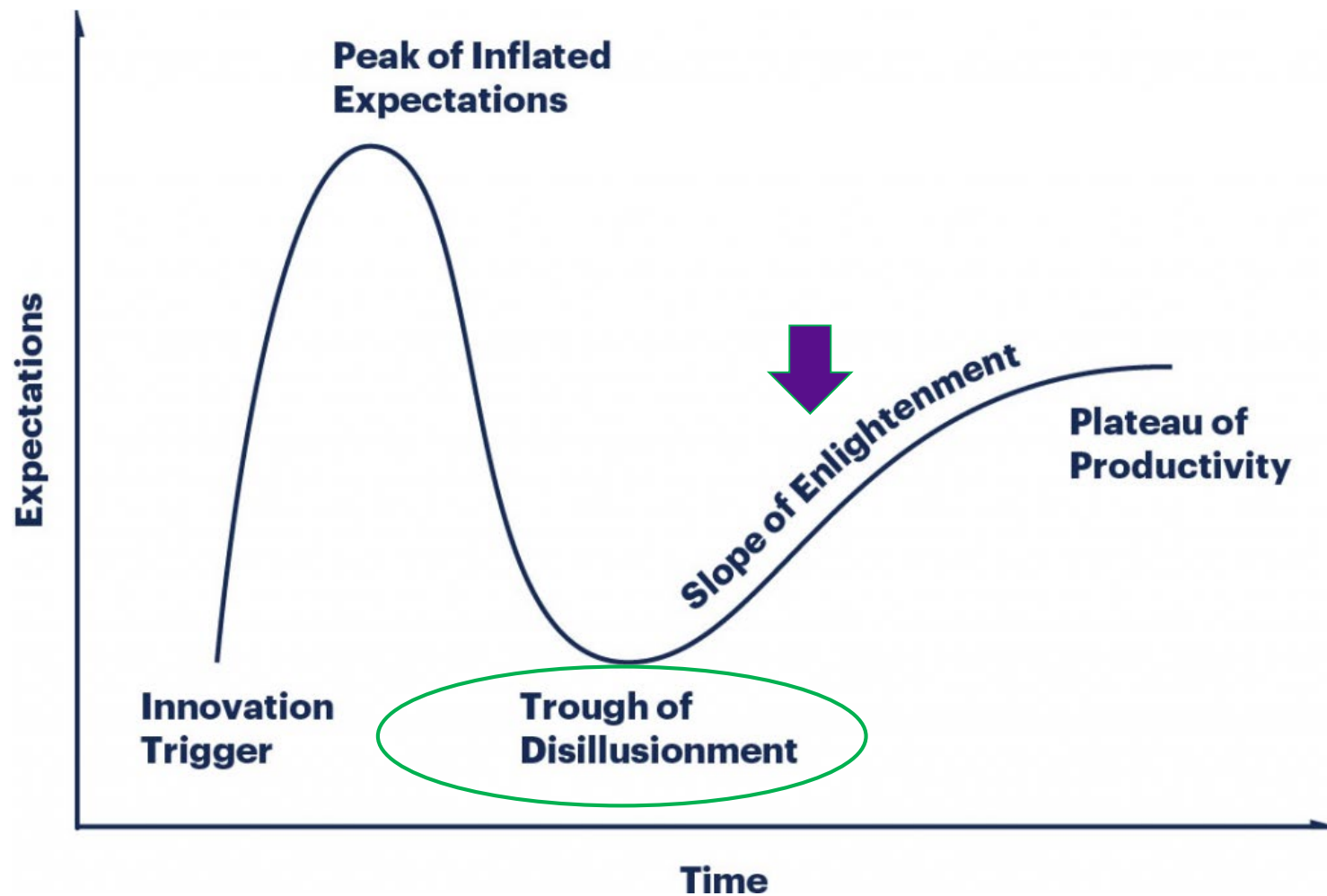




- tDCS applies **weak currents** (1.0 - 4.0 mA) via scalp electrodes placed to modulate brain regions of interest
- tDCS alters neuronal resting membrane potentials, **increasing likelihood of depolarization or hyperpolarization** (without inducing action potentials)
- tDCS is known to induce **mechanisms of synaptic plasticity** (LTP, LTD), production of **neurotrophic factors**

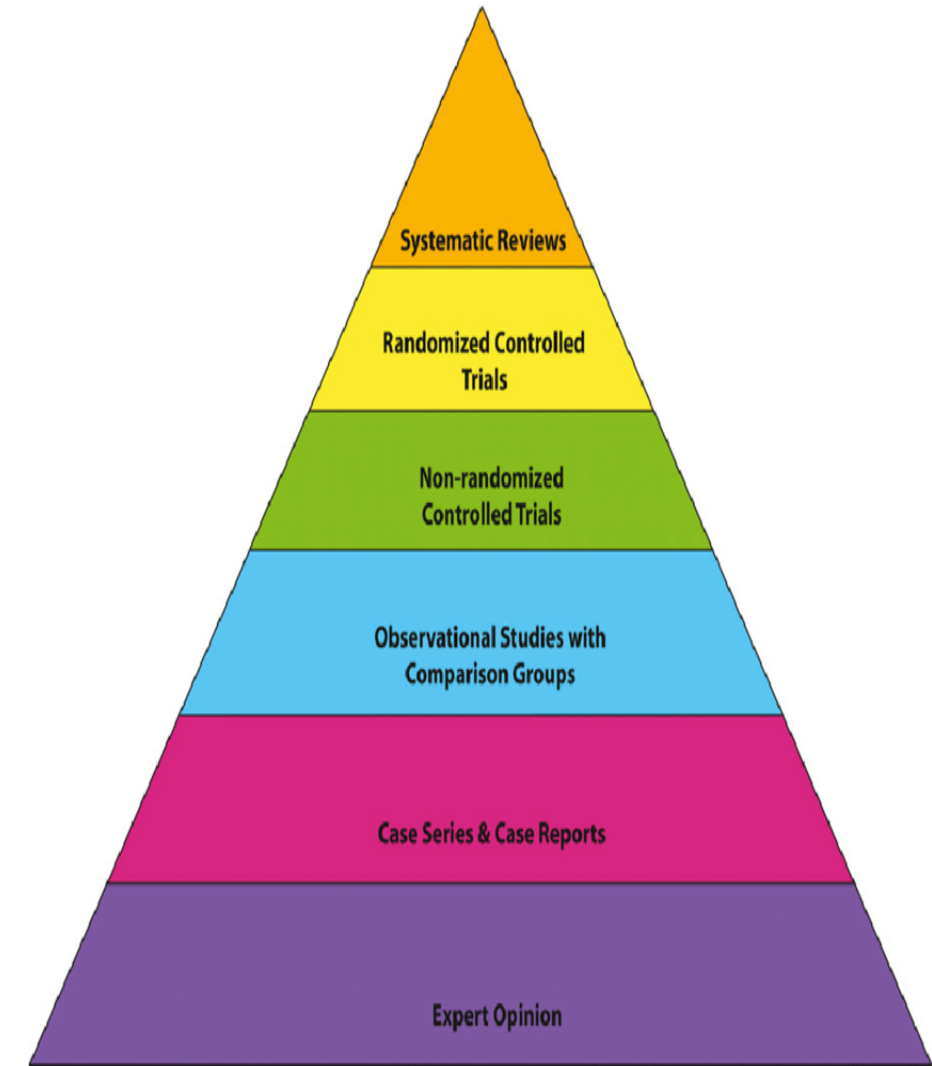


“Hype Cycle”



Level I Evidence is Needed (PRISMA)

Strength of Recommendation	Level of Evidence	Diagnosis/Prognosis/ Treatment
A Definitely Effective	1	Systematic Review of Randomized Controlled Trial
B Probably Effective	2	Systematic Review of Cohort studies, Randomized Controlled Trial, Observational study with dramatic effect, Inception Cohort Study
	3	Systematic Review of Case Control Studies, Non-Randomized Cohort study
C Possibly Effective	4	Case Series, Case Control Studies
D	5	Bench Research



Critical Need for Large RCTs

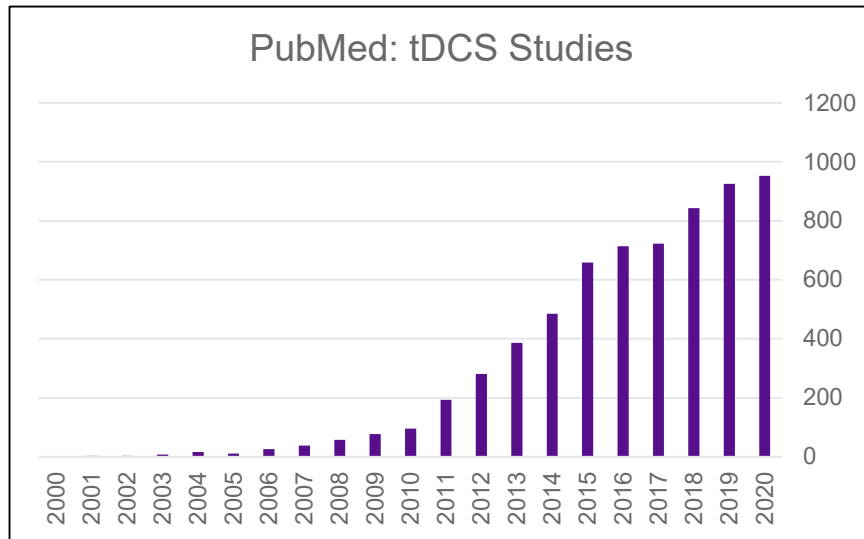
> Int J Neuropsychopharmacol. 2021 Apr 21;24(4):256-313. doi: 10.1093/ijnp/pyaa051.

Evidence-Based Guidelines and Secondary Meta-Analysis for the Use of Transcranial Direct Current Stimulation in Neurological and Psychiatric Disorders

Felipe Fregni¹, Mirret M El-Hagrassy¹, Kevin Pacheco-Barrios^{1 2}, Sandra Carvalho³, Jorge Leite⁴, Marcel Simis⁵, Jerome Brunelin⁶, Ester Miyuki Nakamura-Palacios⁷, Paola Marangolo^{8 9}, Ganesan Venkatasubramanian¹⁰, Daniel San-Juan¹¹, Wolnei Caumo¹², Marom Bikson¹³, André R Brunoni¹⁴, Neuromodulation Center Working Group

Definitely Effective (Level A): Major Depressive Disorder	
*Also very limited evidence to determine “Definitely Not Effective”	MS: Depression
Probably Effective (Level B):	
Pain (neuropathic, fibromyalgia, migraine, post-operative patient-controlled analgesia)	
Chronic and subacute stroke motor rehabilitation	
Epilepsy	
Schizophrenia (auditory hallucinations)	
Cerebellar Ataxia	
Alcohol use disorder (craving/relapse)	
Parkinson’s Disease (motor and cognitive)	
MS (gait)	
Many potential uses remain “Possibly Effective (Level C)”	

Exponential growth in clinical studies...



...BUT clinical conclusions remain limited

- Small sample sizes ($n < 25$) in most reports – many “proof-of-principle” trials
- Too few “doses” administered for optimal evaluation of behavioral effect
 - Many trials reporting effect after only 1 session

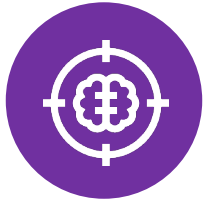
Dosing parameters must be defined and be consistent to reach Level A of evidence



Current intensity/ Current Polarity



Duration of Stimulation



Target Area
Functional/Anatomical



Brain State
Paired Activity drives in a specific way the stimulation



Number/Frequency of Stimulation Sessions

[Hum Brain Mapp.](#) 2019 Feb 15; 40(3): 904–915.
Published online 2018 Oct 30. doi: [10.1002/hbm.24420](#)

PMCID: PMC6387619
EMSID: [EMS81785](#)
PMID: [30378206](#)

Brain state and polarity dependent modulation of brain networks by transcranial direct current stimulation

[Lucia M. Li](#), ¹ [Ines R. Violante](#), ^{1, 2, 3} [Rob Leech](#), ⁴ [Ewan Ross](#), ¹ [Adam Hampshire](#), ¹ [Alexander Opitz](#), ⁵ [John C. Rothwell](#), ² [David W. Carmichael](#), ^{4, 6} and [David J. Sharp](#) ^{2, 1}

> [Brain Stimul.](#) Jan-Feb 2017;10(1):51-58. doi: 10.1016/j.brs.2016.10.001. Epub 2016 Oct 5.

Direct Current Stimulation Modulates LTP and LTD: Activity Dependence and Dendritic Effects

[Greg Kronberg](#) ¹, [Morgan Bridi](#) ², [Ted Abel](#) ³, [Marom Bikson](#) ⁴, [Lucas C Parra](#) ⁴

> [Brain Stimul.](#) Mar-Apr 2020;13(2):287-301. doi: 10.1016/j.brs.2019.10.014. Epub 2019 Oct 18.

Direct current stimulation boosts hebbian plasticity in vitro

[Greg Kronberg](#) ¹, [Asif Rahman](#) ², [Mahima Sharma](#) ², [Marom Bikson](#) ², [Lucas C Parra](#) ²

Trials are challenged by number/frequency of sessions



Current intensity/ Current Polarity



Target Area
Functional/Anatomical



Brain State
Paired Activity drives in a specific way the stimulation

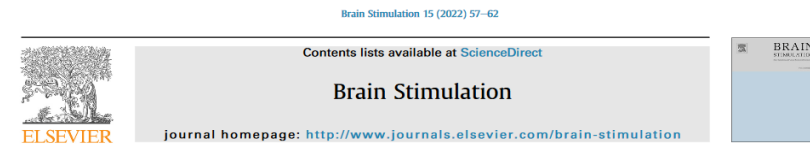


Number/Frequency of
Stimulation Sessions



Duration of Stimulation

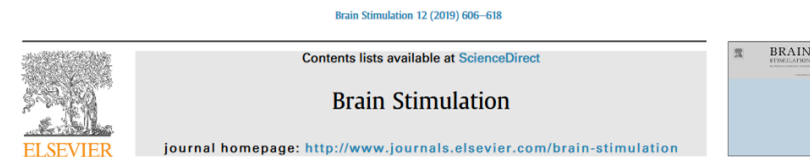
*tDCS is **cumulative**: extended repeated application for adequate evaluation of behavioral effect*



Weak DCS causes a relatively strong cumulative boost of synaptic plasticity with spaced learning

Mahima Sharma ^{*}, Forouzan Farahani, Marom Bikson, Lucas C. Parra

Department of Biomedical Engineering, The City College of New York, CUNY, 160 Convent Avenue, New York, NY, USA



Effects of single-session versus multi-session non-invasive brain stimulation on craving and consumption in individuals with drug addiction, eating disorders or obesity: A meta-analysis

Sensen Song ^{a, b, 1}, Anna Zilverstand ^{c, 1}, Wenjun Gui ^{d, f}, Hui-jie Li ^{e, f}, Xiaolin Zhou ^{a, b, g, h, *}

Example: Many Trials - Limited Conclusions

RCTs of tDCS for Alcohol Use Disorder

Trial	Sample Size	#Sessions	Stimulation	Montage	Tasks (Y/N) ⁺	Outcome
Boggio 2008	13 outpatient	1	2.0 mA, 20 min	L&R DLPFC	N	Lowered AUQ
DaSilva 2013	13 outpatient	5 (1/wk)	2.0 mA, 20 min	L DLPFC	N	Lowered OCDS
den Uyll 2015	41 inpatient	1	1.0 mA, 10 min	L DLPFC	Y	Lowered AAAQ
den Uyll 2016	78 inpatient	3	1.0 mA, 15 min	L DLPFC	Y	No sig. Effect, AAAQ
den Uyll 2017	91 inpatient	4	2.0 mA, 20 min	L&R DLPFC	Y	No sig. Effect, PACS relapse
den Uyll 2018	83 inpatient	4	2.0 mA, 20 min	L&R DLPFC	Y	No sig. Effect, PACS relapse
Holla 2020	15 inpatient	5 (5/w)	2.0 mA, 20 min	L&R DLPFC	N	No sig. Effect, ACQ
Klauss 2014	33 outpatient	5 (5/w)	2.0 mA, 20 min	L&R DLPFC	N	Lowered 6mo relapse
Klauss 2018	45 inpatient	10 (3/w)	2.0 mA, 20 min	L&R DLPFC	N	No sig. effect, OCDS
Vanderhasselt 2020	45 community	1	2.0 mA, 20 min	L&R DLPFC	N	Lowered drinking, No sig. effect AAAQ
Wietschorke 2016	30 inpatient	1	1.0 mA, 20 min	L&R DLPFC	N	No sig. effect, VAS-craving
Claus 2019	79 community	4 (1/wk)	2.0 mA, 20-30 min	R IFG	Y	No sig. effect
Witkiewitz 2019	84 community	8 (1/wk)	2.0 mA, 30 min	R IFG	Y	No sig. effect

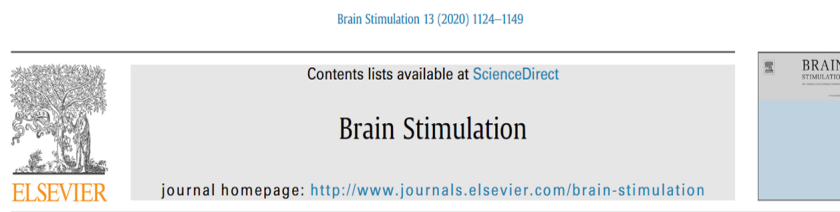


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At-Home Participation: Advantages for RCT Design Include:

- Faster recruitment of larger sample sizes
 - Access for the participants who may benefit the most
- Extended number of tDCS sessions
 - Adequate “dosing” to evaluate behavioral/clinical effect

Research and clinical use needs to continue...



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 Campanella^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 Ghodratiostani^{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 Thielscher^{u,ar}, Nicole Wenderoth^{al}, Ti-Fei Yuan^{as}, Xiaochu Zhang^{at}, Hamed Ekhtiari^{au,*}

Review > Front Hum Neurosci. 2020 Nov 12;14:595567. doi: 10.3389/fnhum.2020.595567.

eCollection 2020.

Update on the Use of Transcranial Electrical Brain Stimulation to Manage Acute and Chronic COVID-19 Symptoms

Giuseppina Pilloni¹, Marom Bikson², Bashar W Badran³, Mark S George^{3,4}, Steven A Kautz^{4,5}, Alexandre Hideki Okano^{6,7}, Abrahão Fontes Baptista^{6,7,8}, Leigh E Charvet¹

Remote supervision allows for the extension of lab standards to the home:

- Monitoring for safety
- Precise dosing
- Reliable electrode placement
- Reproducible results



Brain Stimulation

Volume 13, Issue 3, May–June 2020, Pages 686–693



Supervised transcranial direct current stimulation (tDCS) at home: A guide for clinical research and practice

Leigh E. Charvet ^{a,1}✉, Michael T. Shaw ^{a,b}, Marom Bikson ^c, Adam J. Woods ^d, Helena Knotkova ^{e,f,1}✉

- Training research staff, participants/ caregivers
- Initial and ongoing assessment of participant's capability operating tDCS equipment
- Supportive training procedures and materials
- Simple and fail-safe electrode preparation and positioning
- Strict dose control for each session

Solution for At-Home Research Trials: Remotely Supervised (RS) tDCS

- Extension to deliver tDCS sessions to patients at home maintaining clinical trial standards
- Live supervision via HIPAA-compliant videoconference at each treatment
- Standardized protocol with extensive stop criteria to ensure safety and uniformity

Minimal technical burden for patient:

- tDCS device: Pre-programmed, remotely operated
- Headset: Cap-like, snap sponge electrodes
- Computer/iPad: Remote video visit, digital therapy



RS-tDCS Device Components:

Portable * Wearable * Easy to Use * Controlled Dosing

1x1 Mini-CT tDCS device



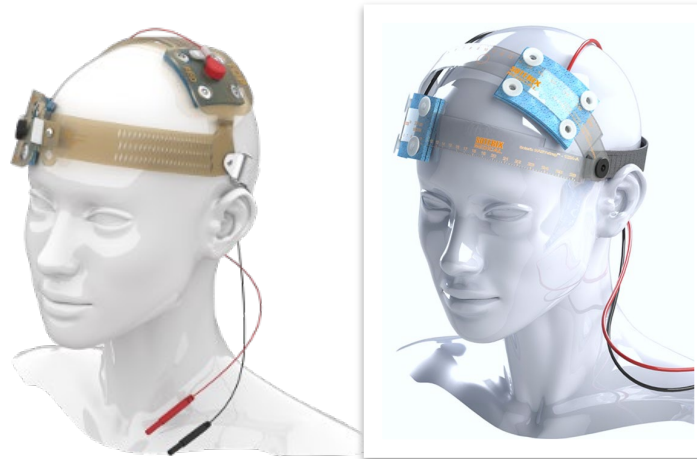
Pre-programmed devices

Dose Control

- Single-use “unlock code” for predetermined “dose”
- Program session type (active or sham), stimulation time and dose

1

SNAPstrap Headgear



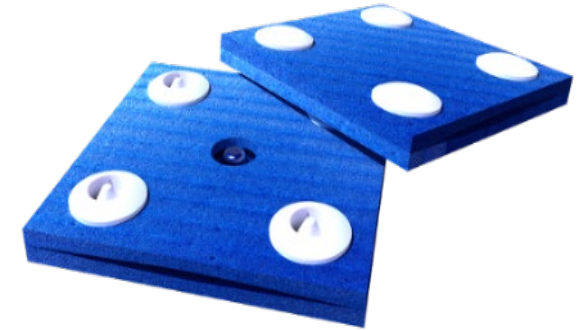
“Cap”-like placement for simple positioning

Uniform electrode placement

- Markers for guidance in placement
- Clear electrode polarity labeling with fixed wiring

2

EASYpad Electrodes



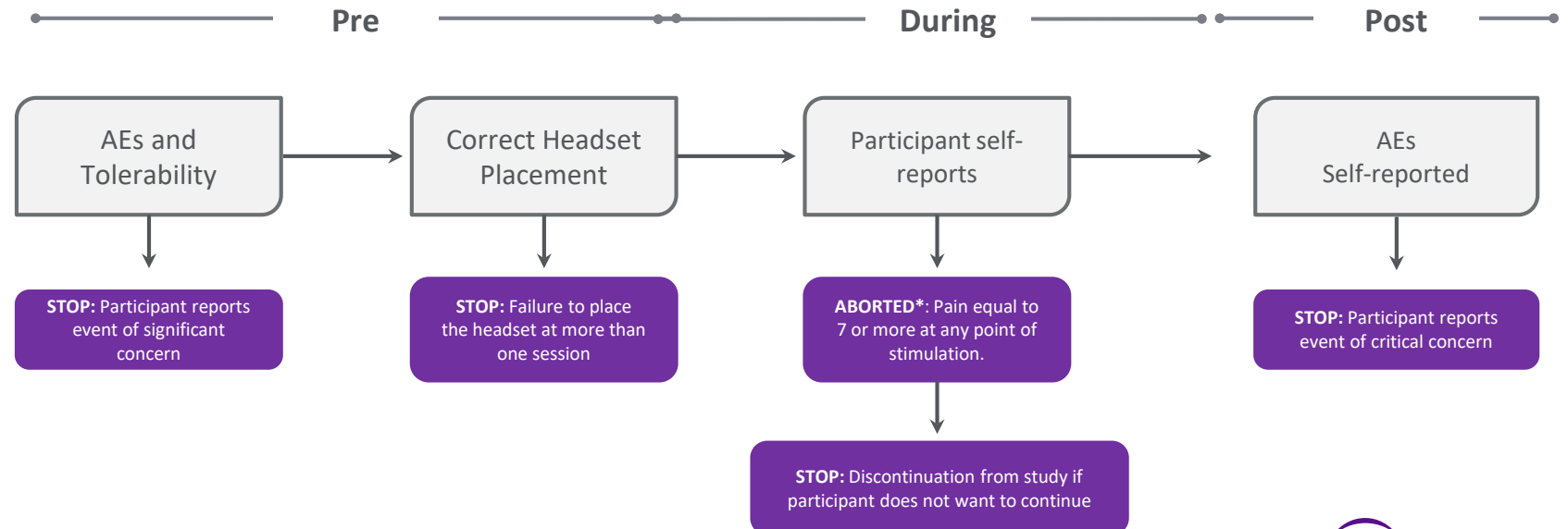
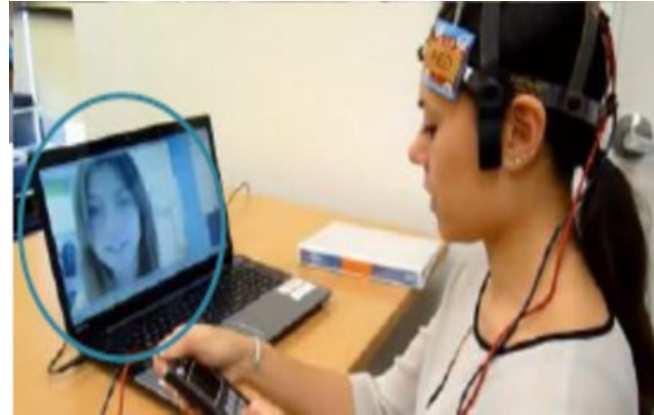
Easy electrode preparation

- Individually-packaged pre-moistened sponges
- Perforated for easy opening
- Snap connectors

3

RS-tDCS: Live Video Supervision

- Laptop computers/iPads
 - Large screens
 - Adaptive mouse (if needed)
 - Background rating scales
- Connected in real-time
 - VSee:
 - HIPAA-compliant
 - Cell-phone backup
- Remote control of computer
 - TeamViewer
 - Initiate videoconferencing
 - Training activities, assessment
- Minimum technical burden
 - Connect to Wi-Fi
 - Open computer



1. Richardson JD, Galletta EE, Charvet L, Shaw M. **Remotely Supervised Transcranial Direct Current Stimulation (RS- tDCS) for People with Stroke-Induced and Progressive Aphasia.** Frontiers in Neurology (under review).
2. Eilam-Stock T, George A, Charvet L. **Cognitive telerehabilitation with transcranial direct current stimulation (tDCS) improves cognitive and emotional functioning following a traumatic brain injury: A case study.** Archives of Clinical Neurology (in press).
3. Bikson M, Hanlon C, Woods AJ, Gillick BT, Charvet L, et al. **Guidelines for Operationalizing TMS/tES through the COVID-19 Pandemic.** Brain Stimulation 13 (4), 1124-1149.
4. Charvet LE, Shaw MT, Bikson M, Woods A, Knotkova H. **Supervised transcranial direct current stimulation (tDCS) at home: A guide for clinical research and practice.** Brain Stimulation. Volume 13, Issue 3, May–June 2020, 686-693.
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7. Pilloni G, Shaw M, Charvet L. **Remotely supervised transcranial direct current stimulation (tDCS) improves cognitive and emotional functioning following a traumatic brain injury: A case study.** Archives of Clinical Neurology (in press).
8. Vitorio R, Stuart S, Charvet L. **Remotely supervised transcranial direct current stimulation (tDCS) at home: A guide for clinical research and practice.** Brain Stimulation. Volume 13, Issue 3, May–June 2020, 686-693.
9. Dobbs B, Pawlak M, Charvet L. **Feasibility and benefits of transcranial direct current stimulation (tDCS) in multiple sclerosis: A pilot study.** Frontiers in Neurology. 2019 Jul 15;12:576223X10964820. doi: 10.3389/fnrg.2019.00576. PubMed PMID: 3140964820.
10. Agarwal S, Pawlak M, Charvet L. **Feasibility and benefits of transcranial direct current stimulation (tDCS) in multiple sclerosis: A pilot study.** Frontiers in Neurology. 2019 Jul 15;12:576223X10964820. doi: 10.3389/fnrg.2019.00576. PubMed PMID: 3140964820.
11. Bikson M, Brunoni AR, Charvet L, et al. **Remotely supervised transcranial direct current stimulation (tDCS) at home: A guide for clinical research and practice.** Brain Stimulation. Volume 13, Issue 3, May–June 2020, 686-693.
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13. Shaw MT, Kasschau M, Charvet L. **Remotely supervised transcranial direct current stimulation (tDCS) at home: A guide for clinical research and practice.** Brain Stimulation. Volume 13, Issue 3, May–June 2020, 686-693.
14. Charvet LE, Dobbs B, Charvet L. **Remotely supervised transcranial direct current stimulation (tDCS) at home: A guide for clinical research and practice.** Brain Stimulation. Volume 13, Issue 3, May–June 2020, 686-693.
15. Charvet L, Shaw M, Dobbs B, Frontario A, Sherman K, Bikson M, Datta A, Krupp L, Zeinapour E, Kasschau M. **Remotely Supervised Transcranial Direct Current Stimulation Increases the Benefit of At-Home Cognitive Training in Multiple Sclerosis.** Neuromodulation. 2018 Jun;21(4):383-389. doi: 10.1111/ner.12583. Epub 2017 Feb 22. PubMed PMID: 28225155; PubMed Central PMCID: PMC5975186.
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RS-tDCS Developed in Collaboration with People With MS: Generalizable for Use Across Conditions

Diversity of MS can inform symptom management and rehabilitation across conditions:

- Demographically diverse – lifespan disorder
- Range of disability levels – minimal to severe
- Variability in symptoms=cognitive/motor/psychological

telerehabilitation benefits

reduces symptoms

PMCID:6425598.

leads to optimal

on (tDCS):

PMCID:

cognitive training in

, et al.. Rigor

in a Patient With

Update on

sclerosis:

PMCID:37310; PubMed

At-Home Treatment: Saves Time and Money, Reaching More Patients

For those with homes within NYC:

Average visit travel time

1.28 hours

Average visit transportation cost

\$15.60



Reaching **MANY** more
people living with MS



For those with homes outside of
NYC (NJ/CT/Long Island):

Average visit travel time

3.5 hours

Average visit transportation cost

\$45.00



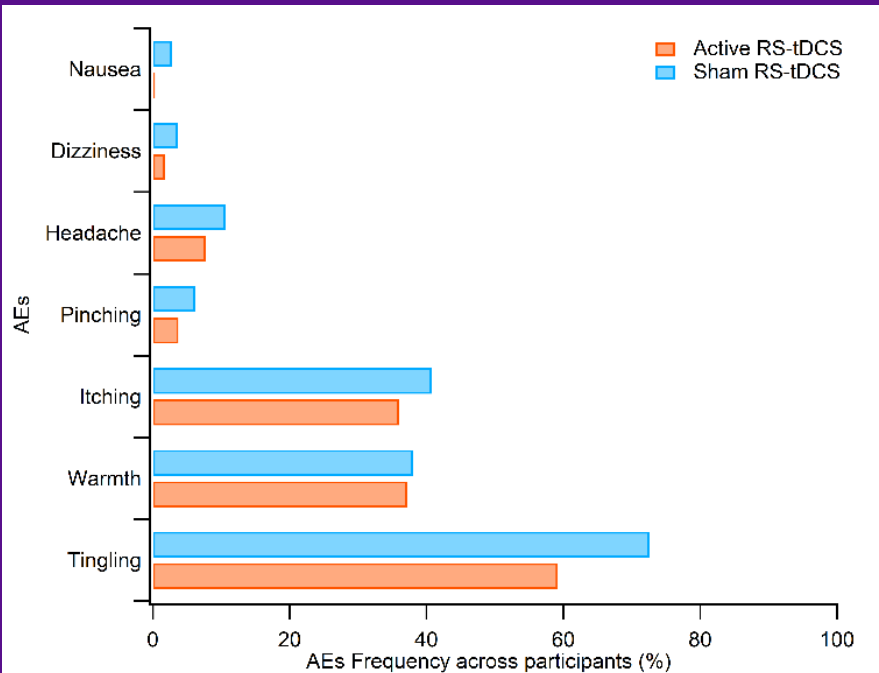
► J Telemed Telecare. 2021 Jan;27(1):39-45. doi: 10.1177/1357633X19861830. Epub 2019 Jul 15.

Telerehabilitation benefits patients with multiple sclerosis in an urban setting

Michael T Shaw ¹, Pamela Best ¹, Ariana Frontario ², Leigh E Charvet ¹

1. Why tDCS? The unmet need of MS symptom burden
2. tDCS overview
3. Our approach with participation from home: Remotely Supervised (RS)-tDCS
4. **RS-tDCS studies in MS**

RS-tDCS: Safe, Tolerable, Feasible

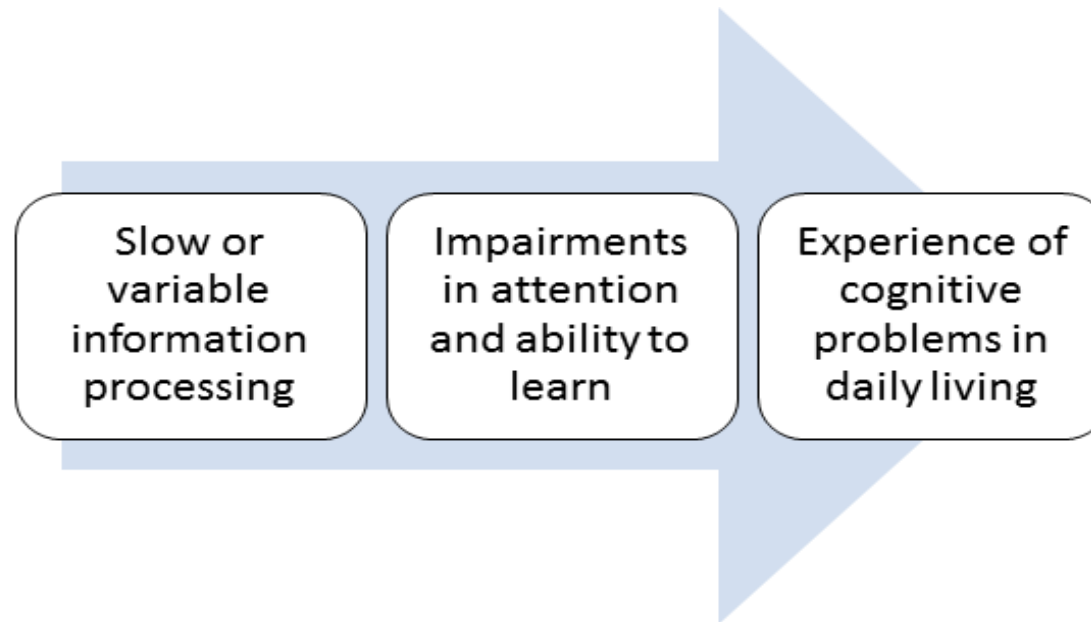


Pilloni et al., under review

- 6 sham-controlled RCTs and open label active trials
- n=308 participants (91% MS)
- 6,779 sessions
 - **TOLERABLE:**
 - n=1/308 failed the tolerability test at study entry
 - AEs rated on the VAS pain > 7 occurred in 27/6779 RS-tDCS sessions
 - 3/6779 (0.04%) sessions were aborted due to tolerability
 - No session-limiting AE resulted in study discontinuation
 - **FEASIBLE:**
 - Ages 18-78
 - Minimal to Moderate/Severe Disability (EDSS 0-7.5)

COGNITIVE FUNCTIONING IN MS

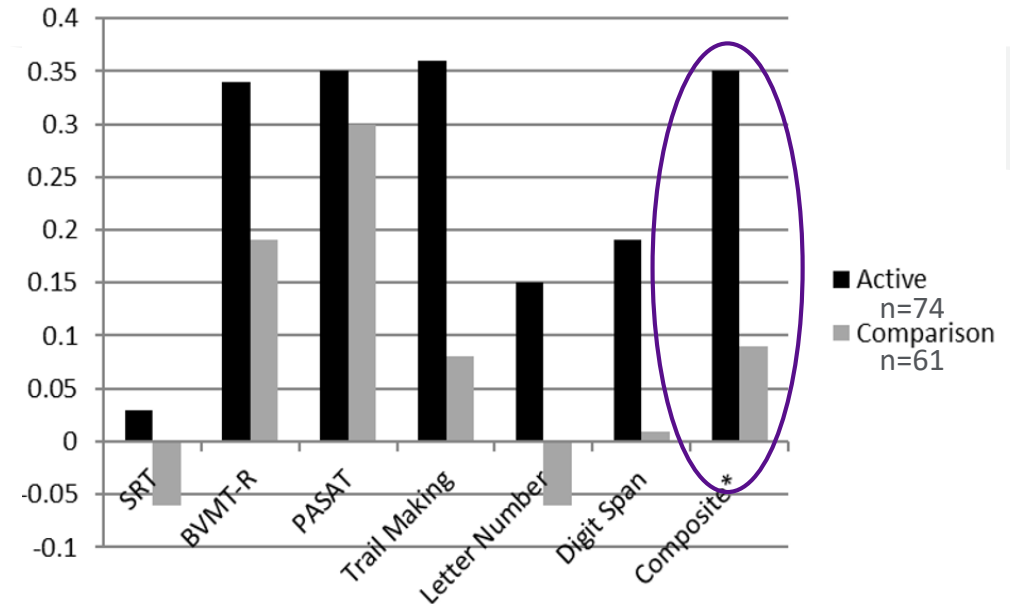
- >75% of all people living with MS
- Typically “mild”, led by slowed information processing speed
- Typically progresses “slowly” over time to include new learning



Deluca, Chiaravalloti & Sandroff, 2020

Adaptive Cognitive Training Improves Cognitive Functioning in MS

- At-home, remotely monitored
- n=135 MS, mild-moderate cognitive impairment
- 60 hours x 12 weeks
 - Posit BrainHQ vs. computer game control
- Rapid recruitment- 20 months enrollment
- High rates of completion:
 - n=130/135 completers
 - 68% compliance with training



Randomized Controlled Trial > PLoS One. 2017 May 11;12(5):e0177177.

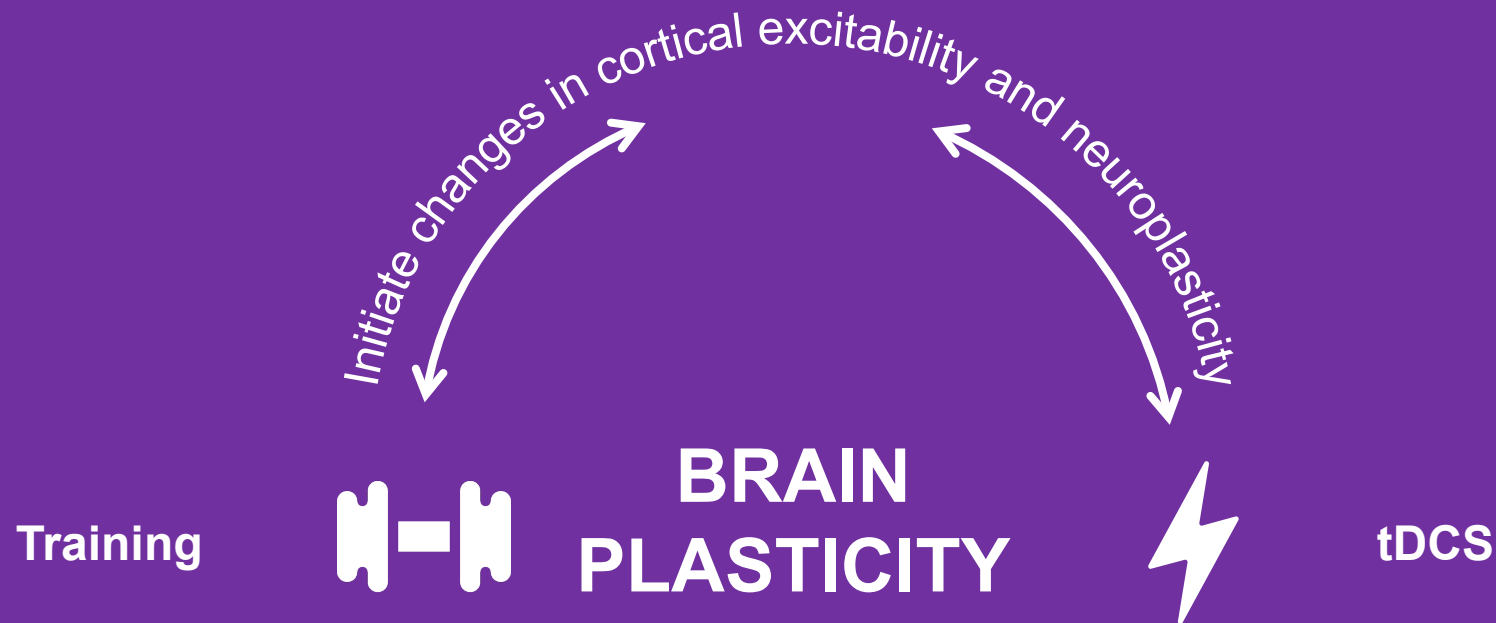
doi: 10.1371/journal.pone.0177177. eCollection 2017.

Cognitive function in multiple sclerosis improves with telerehabilitation: Results from a randomized controlled trial

Leigh E Charvet¹, Jie Yang², Michael T Shaw¹, Kathleen Sherman¹, Lamia Haider³, Jianjin Xu⁴, Lauren B Krupp¹

Can we “boost” rehabilitation?

Potential synergistic effect of tDCS and training



[Hum Brain Mapp.](#) 2019 Feb 15; 40(3): 904–915.
Published online 2018 Oct 30. doi: [10.1002/hbm.24420](#)

PMCID: [PMC6387619](#)
EMSID: [EMS81785](#)
PMID: [30378206](#)

Brain state and polarity dependent modulation of brain networks by transcranial direct current stimulation

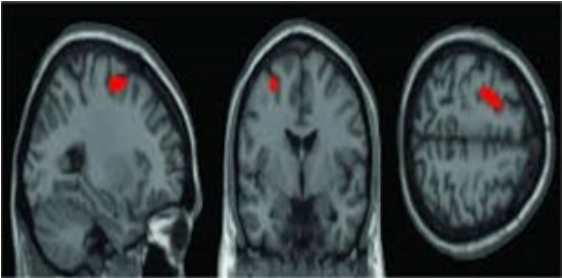
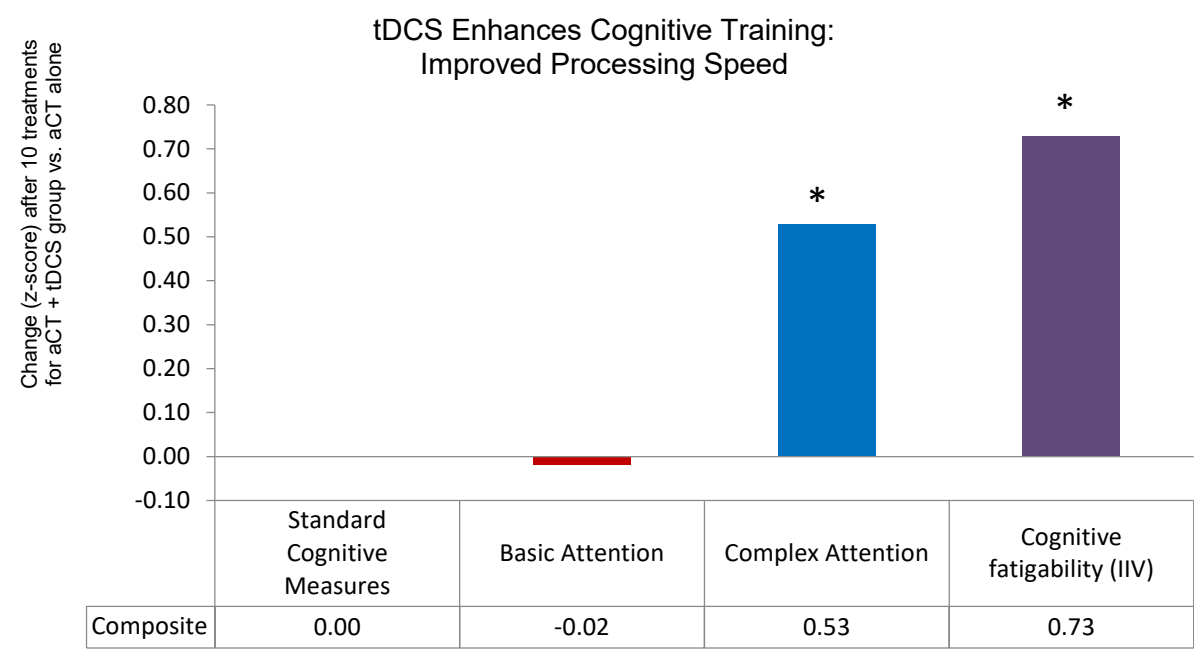
[Lucia M. Li](#),¹ [Ines R. Violante](#),^{1, 2, 3} [Rob Leech](#),⁴ [Ewan Ross](#),¹ [Adam Hampshire](#),¹ [Alexander Opitz](#),⁵ [John C. Rothwell](#),² [David W. Carmichael](#),^{4, 6} and [David J. Sharp](#)⁰¹

> [Brain Stimul.](#) Jan-Feb 2017;10(1):51-58. doi: [10.1016/j.brs.2016.10.001](#). Epub 2016 Oct 5.

Direct Current Stimulation Modulates LTP and LTD: Activity Dependence and Dendritic Effects

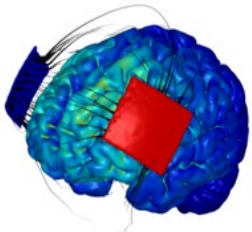
[Greg Kronberg](#)¹, [Morgan Bridi](#)², [Ted Abel](#)³, [Marom Bikson](#)⁴, [Lucas C Parra](#)⁴

RS-tDCS Paired with Cognitive Training



Buschkuehl et al. 2014

Functional Targeting with tDCS



Seibt et al. 2016

[Neuromodulation](#). Author manuscript; available in PMC 2018 Jul 5.
Published in final edited form as:
[Neuromodulation](#). 2018 Jun; 21(4): 383–389.
Published online 2017 Feb 22. doi: [10.1111/ner.12583](#)

Remotely Supervised Transcranial Direct Current Stimulation Increases the Benefit of At-Home Cognitive Training in Multiple Sclerosis

[Leigh Charvet](#), PhD,* [Michael Shaw](#), BS,* [Bryan Dobbs](#), BS,* [Ariana Frontario](#), BS,† [Kathleen Sherman](#), MS,*
[Marom Bikson](#), PhD,‡ [Abhishek Datta](#), PhD,§ [Lauren Krupp](#), MD,* [Esmail Zeinapour](#), MS,‡ and [Margaret Kasschau](#), BS¶

tDCS for Fatigue?

- Overwhelming sense of tiredness, lack of energy, feeling of exhaustion
 - Distinct from weakness, depression, sleepiness
 - 85% report fatigue among their most disabling problems
 - 10-20% report it to be their worst symptom
 - Interferes significantly with daily functioning
- Major unmet treatment need



Review > [J Neurol Sci.](#) 2017 Sep 15;380:256-261. doi: 10.1016/j.jns.2017.07.042. Epub 2017 Jul 28.

Pharmacological treatments for fatigue in patients with multiple sclerosis: A systematic review and meta-analysis

Ting-Ting Yang¹, Li Wang², Xiao-Yang Deng³, Gang Yu⁴

> [Lancet Neurol.](#) 2021 Jan;20(1):38-48. doi: 10.1016/S1474-4422(20)30354-9. Epub 2020 Nov 23.

Safety and efficacy of amantadine, modafinil, and methylphenidate for fatigue in multiple sclerosis: a randomised, placebo-controlled, crossover, double-blind trial

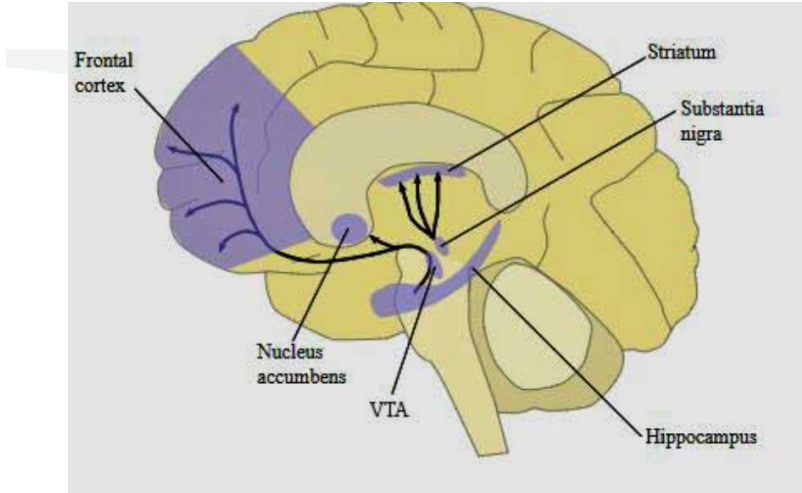
Bardia Nourbakhsh¹, Nisha Revirajan², Bridget Morris³, Christian Cordano², Jennifer Creasman⁴, Michael Manguinao², Kristen Krysko², Alice Rutatangwa², Caroline Auvray², Salman Aljarallah³, Chengshi Jin⁴, Ellen Mowry⁵, Charles McCulloch⁴, Emmanuelle Waubant²

Dorsolateral Prefrontal Cortex: Target in Fatigue Circuit?

> *Mult Scler.* 2019 Apr;25(4):554-564. doi: 10.1177/1352458518758911. Epub 2018 Feb 21.

Multiple sclerosis-related fatigue: Altered resting-state functional connectivity of the ventral striatum and dorsolateral prefrontal cortex

Sven Jaeger¹, Friedemann Paul², Michael Scheel¹, Alexander Brandt¹, Josephine Heine³, Daniel Pach⁴, Claudia M Witt⁴, Judith Bellmann-Strobl⁵, Carsten Finke⁶



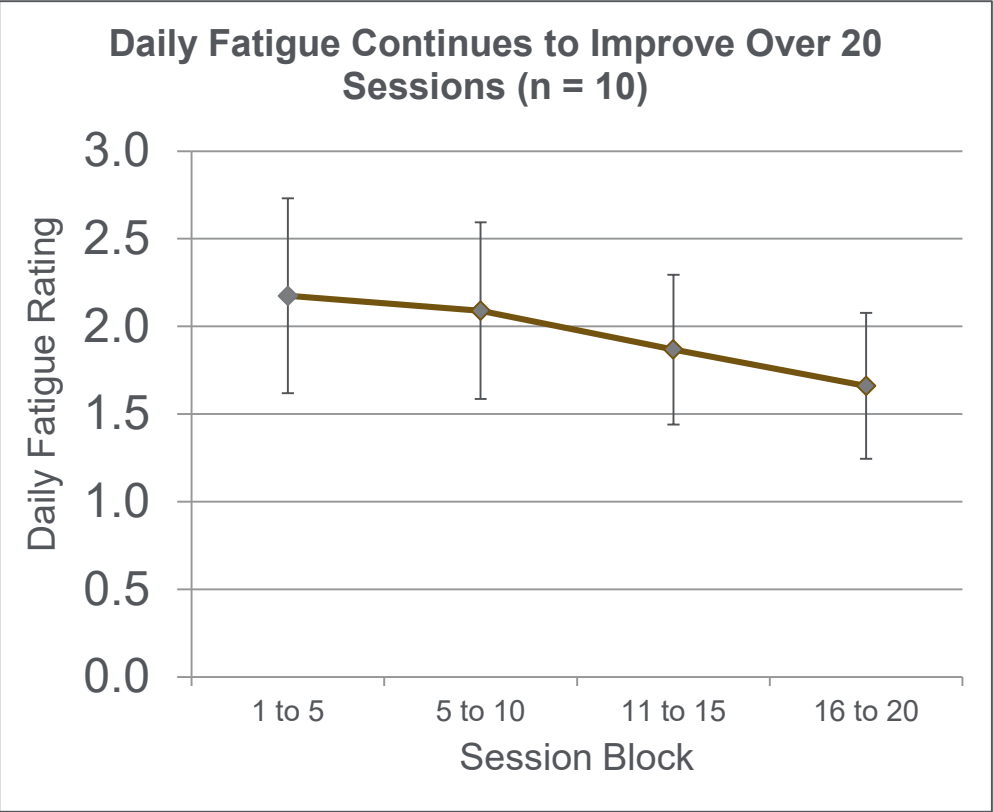
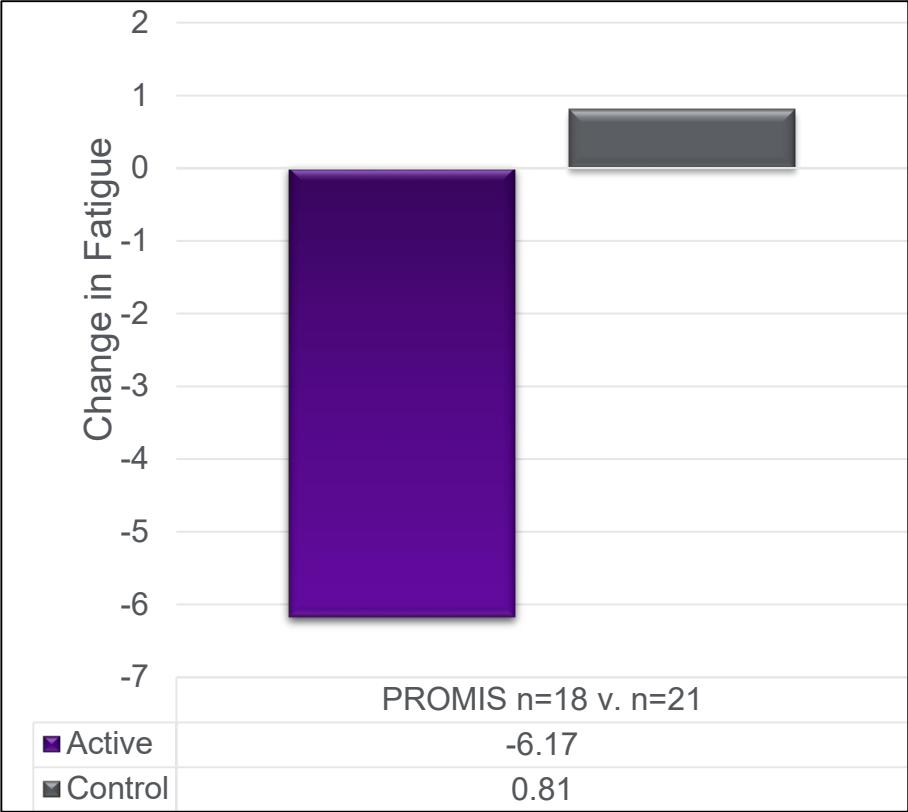
Regional microglial activation in the substantia nigra is linked with fatigue in MS

Tarun Singhal, Steven Cicero, Hong Pan, Kelsey Carter, Shipra Dubey, Renxin Chu, Bonnie Glanz, Shelley Hurwitz, Shahamat Tauhid, Mi-Ae Park, Marie Kijewski, Emily Stern, Rohit Bakshi, David Silbersweig, Howard L. Weiner

First published August 7, 2020, DOI: <https://doi.org/10.1212/NXI.0000000000000854>

Author (Year)	N	Design	#Sessions, Treatment Montage
Accler et al. (2013) ⁷³	32 (Post-polio)	Sham vs. active	15 sessions x 1.5 mA motor cortex x 15 minutes
Ferrucci et al. (2014) ⁶³	25 (MS)	Sham-controlled, crossover	5 sessions x 1.5 mA motor cortex x 15 minutes
Saiote et al. (2014) ⁶²	13 (MS)	Sham-controlled, crossover	5 sessions x 1.0 mA DLPFC x 20 minutes
Tecchio et al. (2014) ⁶⁰	10 (MS)	Sham-controlled, crossover	5 sessions x 1.5 mA sensorimotor cortex 15 minutes
Forogh et al. (2016) ⁷⁴	23 (Parkinson's)	Randomized sham vs. active	8 sessions x 0.6 A/m2A DLPFC x 20 minutes
Chalah et al. (2017) ⁷¹	10 (MS)	Sham-controlled, crossover	5 sessions x 2.0mA DLPFC or PPC x 20 minutes

Pilot RCT: tDCS Significantly Reduces MS Fatigue



IDLFPC, 20 sessions x 2.0 mA vs. sham

Remotely supervised transcranial direct current stimulation for the treatment of fatigue in multiple sclerosis: Results from a randomized, sham-controlled trial

Leigh E Charvet, Bryan Dobbs, Michael T Shaw, more...

[Show all authors](#)

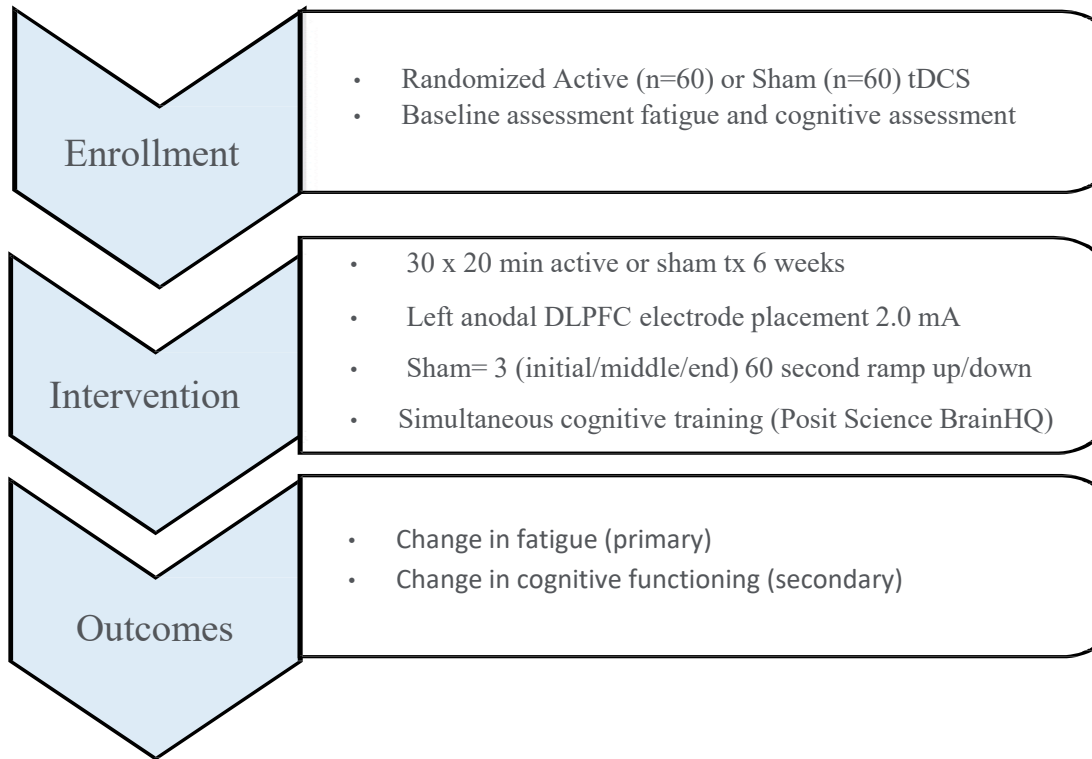
First Published September 22, 2017 | Research Article |

[Check for updates](#)

<https://doi.org/10.1177/1352458517732842>



tDCS for the Management of MS-Related Fatigue

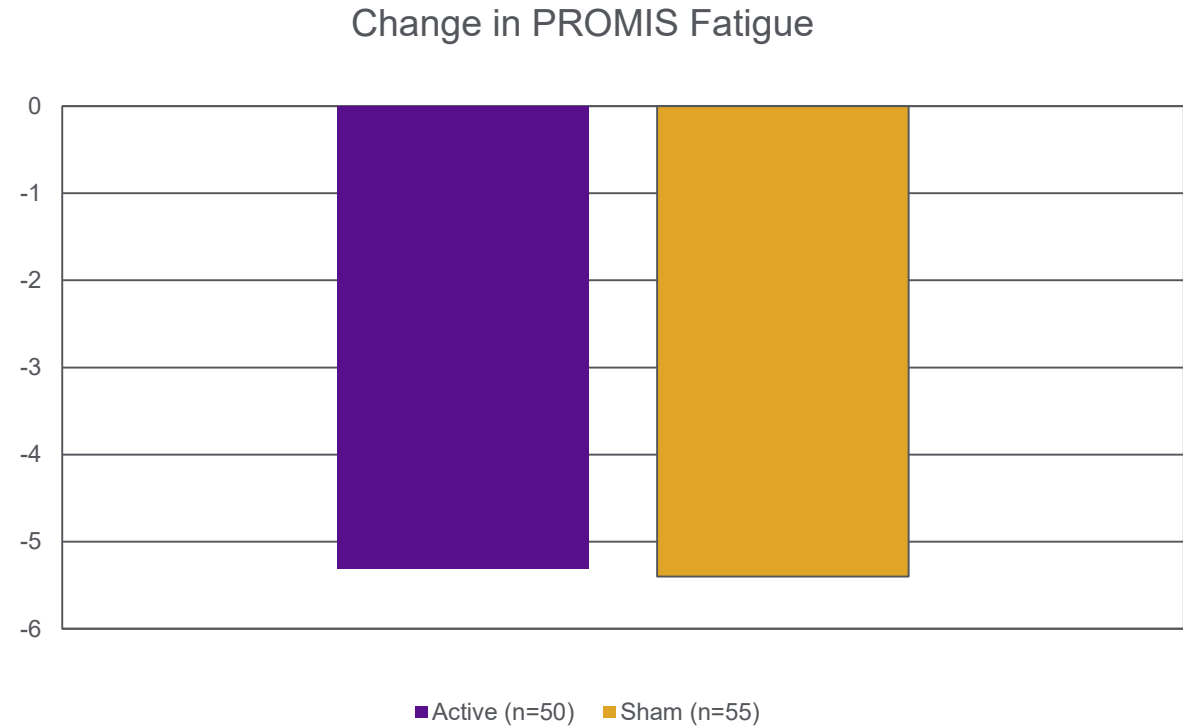


- **Enrollment:**
 - **Total n=120 enrolled** (22 months)
 - Ages 20 to 68 years
 - Minimal to moderate neurological impairment
 - **Fatigue at entry (FSS)**
 - Screened out for depression (BDI)
 - Screened out for severe cognitive impairment (SDMT)
- **Compliance with 30 session protocol:**
 - **92%** of the participants completed >25 sessions

National MS Society; NCT03838770

Preliminary RCT Results: Fatigue

- PROMIS Fatigue
- Both active and sham group significantly improved from baseline to treatment end
- No significant difference in active vs. sham change in fatigue



Preliminary findings: **Considerations for fatigue outcomes**

- Differs from pilot findings
- Depression/distress mediating pilot findings of benefit?
- Role of cognitive training?
- Stimulation in sham?
- Consistent with fatigue research to date:
 - Medications not superior to placebo, with more AEs
 - tDCS active vs. sham tolerability profile:
 - Implications for clinical use?

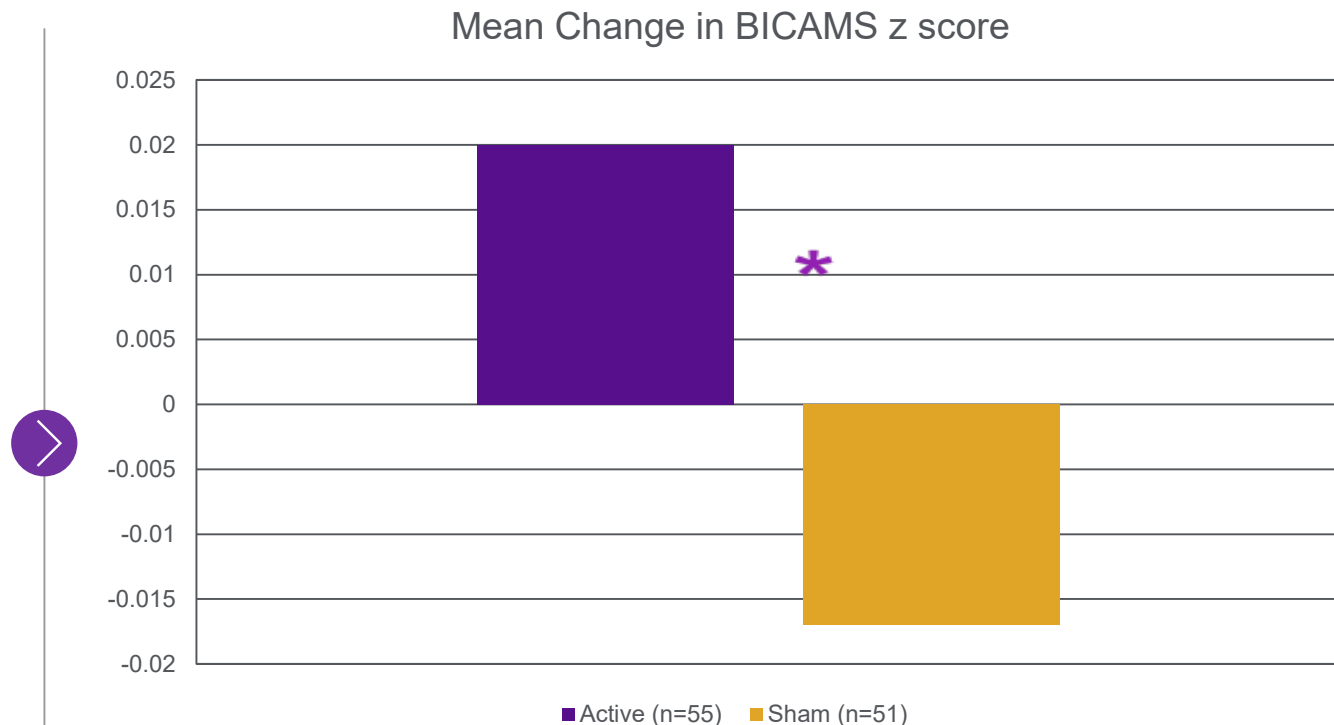
› [Mult Scler Relat Disord.](#) 2021 Sep;54:103129. doi: 10.1016/j.msard.2021.103129. Epub 2021 Jul 3.

Ethical considerations in the treatment of multiple sclerosis fatigue

Bardia Nourbakhsh ¹, Emmanuelle Waubant ², Andrea W M Evers ³, Andrew J Solomon ⁴

Preliminary RCT Results: Cognitive

- BICAMS: Brief International Cognitive Assessment in MS
 - SDMT
 - RAVLT
 - BVMT-R
- Only active group significantly improved from baseline to treatment end
- Active significantly greater cognitive improvement vs. sham outcomes



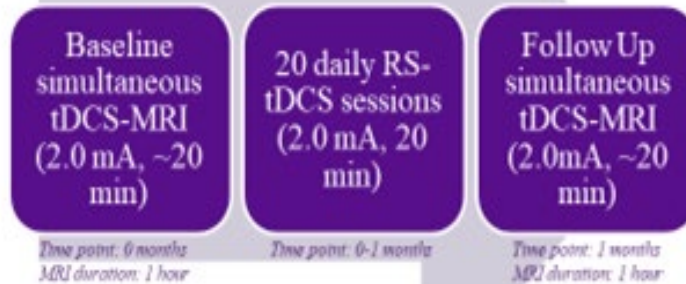
Preliminary findings: **Considerations for Cognitive Outcomes**

- Confirms pilot findings
- Benefit in sample not selected for cognitive impairment
 - Majority of people with MS have some cognitive involvement
 - Processing speed underlies cognitive functions
- 30 days x 20 min with tDCS – vs 60 day x 60 min without
 - Potentiate benefits of cognitive training?

In vivo assessment of tDCS-induced neuronal responses

NIH R21NS101712-01 (Ge & Charvet)

Imaging and Treatment Overview



Imaging Markers of tDCS Response:
Cognitive and Symptom Outcomes

Pending Analyses:

n=31 MS

n=32 Healthy Controls

Study Design: Simultaneous MRI-tDCS System



The session consists of:

- ~ 20 mins of baseline MRI (headset on, no stimulation)
- ~ 20 mins of active tDCS + MRI

tDCS (Soterix, Inc.)

- 2.0 mA
- Left dorsolateral prefrontal cortex

T2-based TRUST sequence

- Cerebral blood flow (CBF)
- Cerebral metabolic rate of oxygen (CMRO2)

tDCS Functional Targeting for Motor Recovery?

Multiple factors contributing to lower and upper extremity dysfunction

“Boost” known benefits of aerobic physical activity in MS for functional mobility

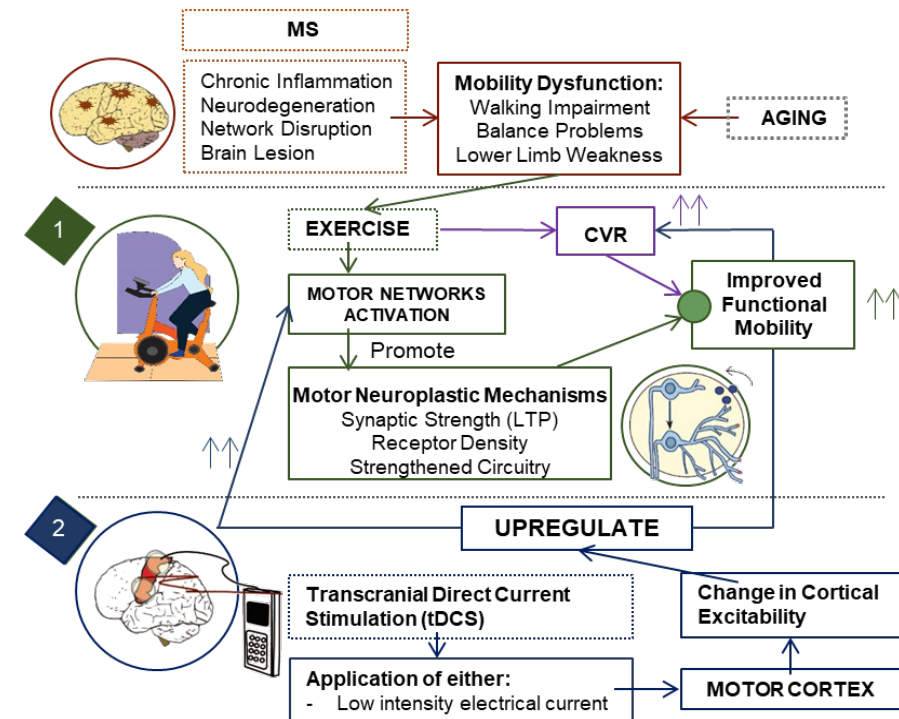
Increase neural plasticity mechanisms in rehabilitative training

- Provoking changes at the functional and structural level of brain organization
- 2019

Sandroff and Motl, 2018; Prosperini and Di Filippo, 2019

Tomassini V, Matthews PM, Thompson AJ, et al. Neuroplasticity and functional recovery in multiple sclerosis. Nat Rev Neurol. 2012

Leocani L, Chieffo R, Gentile A, Centonze D. Beyond rehabilitation in MS: Insights from non-invasive brain stimulation. Mult Scler. 2019;25(10):1363-1371.



Adapted from El-Sayes et al. 2019

Pilot: tDCS+Aerobic Exercise for Walking Impairments in MS: Randomized, double-blind, sham controlled, parallel arm pilot study



Giuseppina Pilloni, PhD

Study design

Randomized, double-blind, sham controlled, parallel arm pilot study

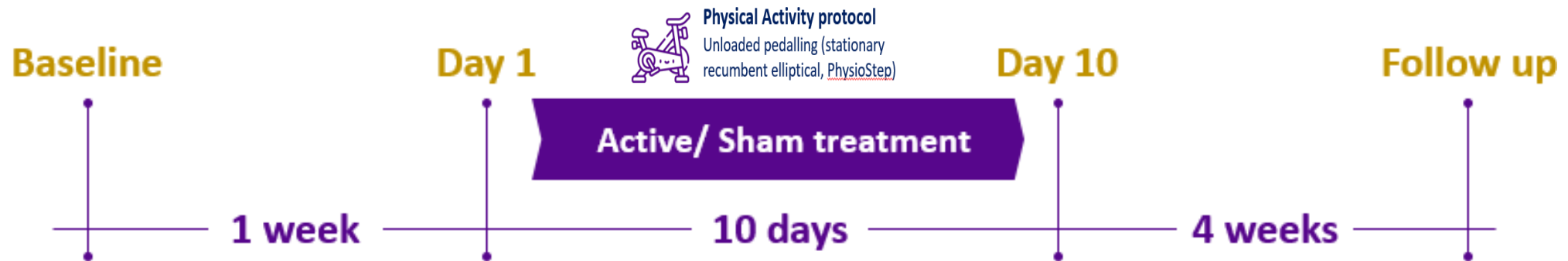
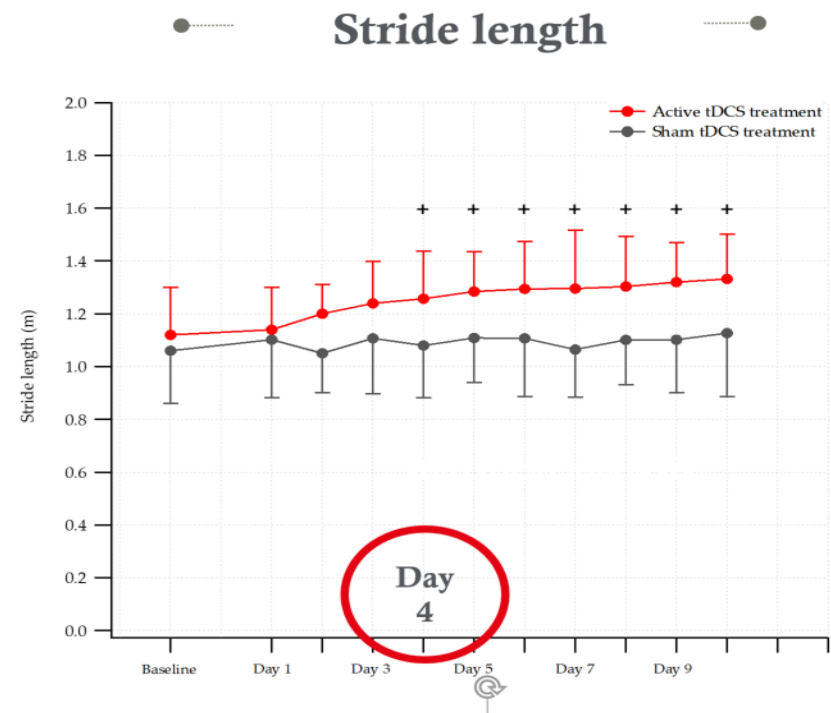
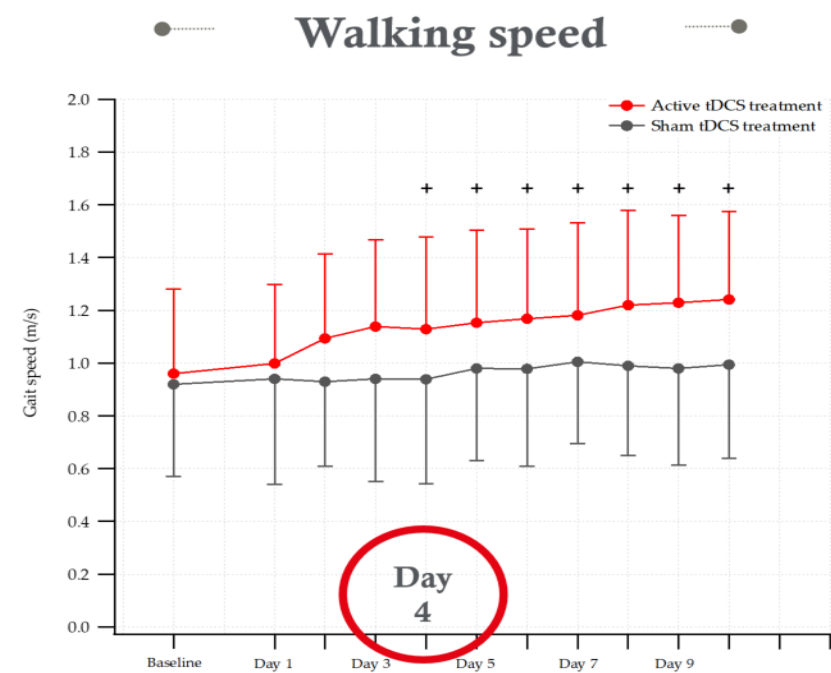


Figure 1: Timeline of the study

Significant benefit with repeated sessions



Research Article | Open Access | CC BY-NC-ND

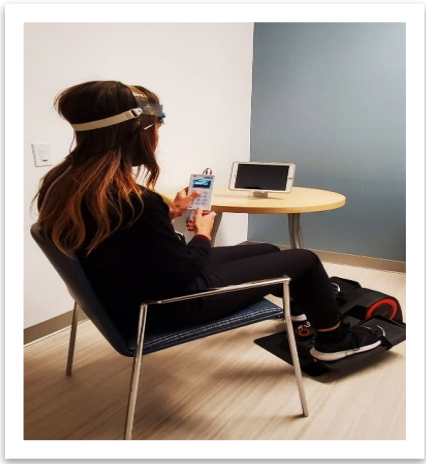
Walking in multiple sclerosis improves with tDCS: a randomized, double-blind, sham-controlled study

Giuseppina Pilloni, Claire Choi, Michael T Shaw, Giancarlo Coghe, Lauren Krupp, Marilyn Moffat, Eleonora Cocco, Massimiliano Pau, Leigh Charvet

First published: 20 October 2020 | <https://doi.org/10.1002/acn3.51224>

RCT to Follow Pilot Using RS-tDCS

- At-home aerobic exercise to improve gait and balance using RS-tDCS
- Structured program of aerobic exercise + tDCS
- Remote gait assessment



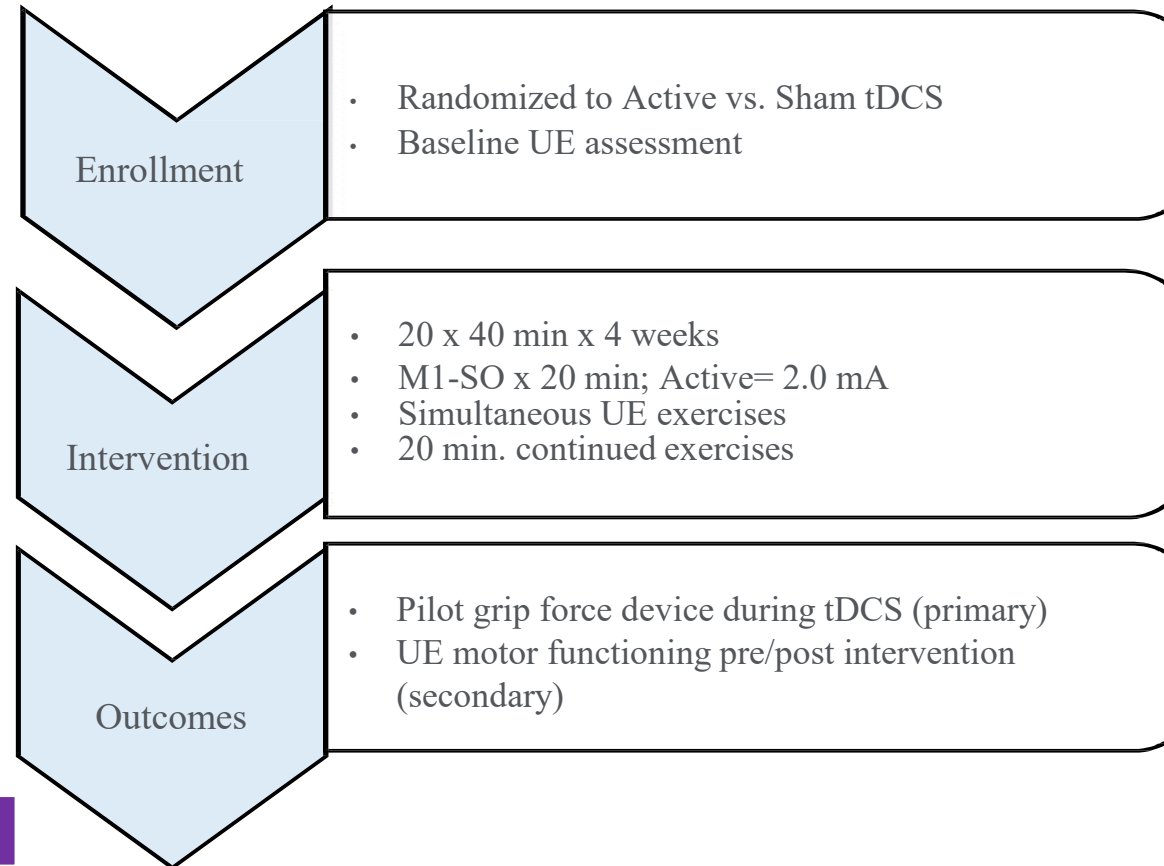
A Pilot Trial of Remotely-Supervised Transcranial Direct Current Stimulation (RS-tDCS) to Enhance Motor Learning in Progressive MS

- **Sample Size Enrollment:**

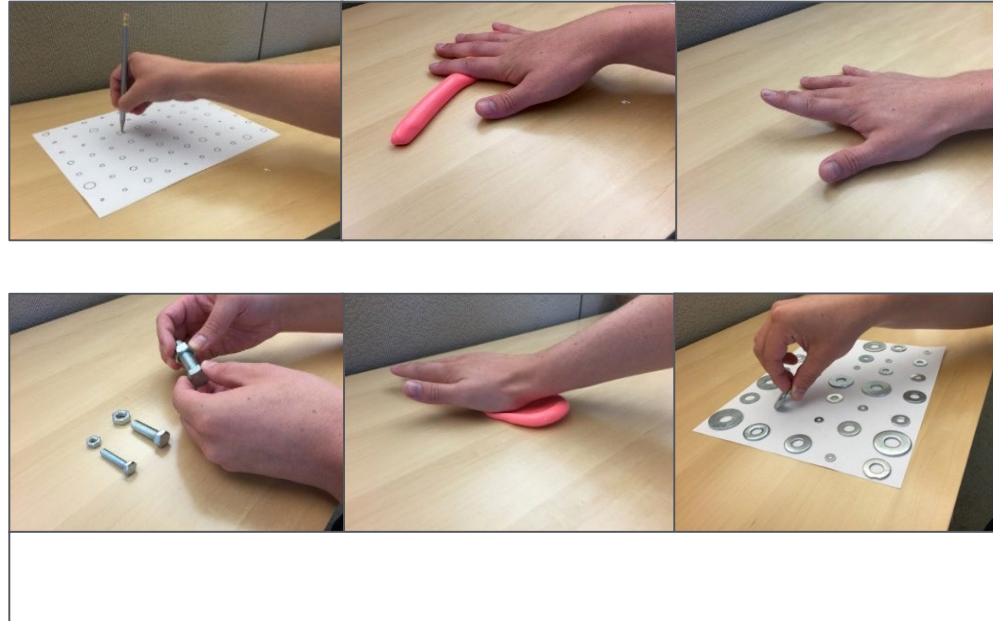
- Total n=66 enrolled (30 months)
- Progressive MS
- Moderate to severe neurological impairment
- Manual dexterity impairment at entry (9HPT)

- **Compliance for Extended Treatment:**

- 98% of the participants completed >18 sessions



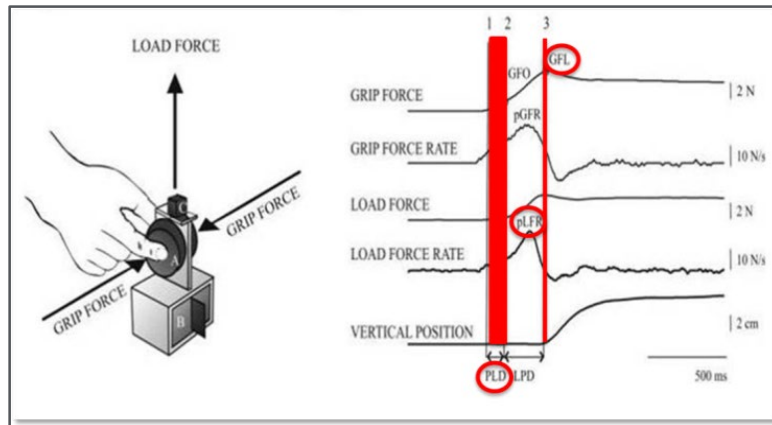
US DoD; NCT03499314



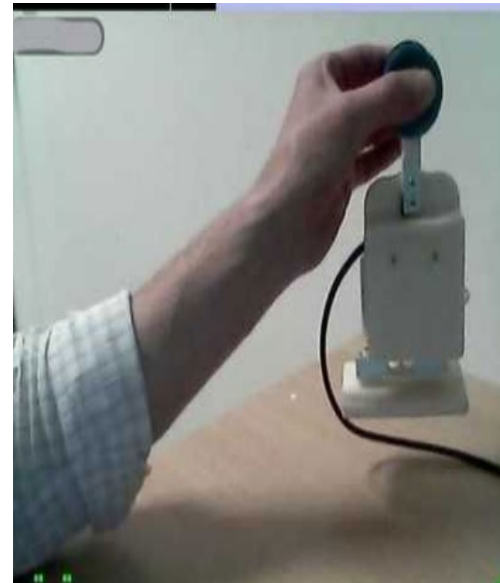
Randomized Controlled Trial > Mult Scler. 2015 Oct;21(12):1546-56.
doi: 10.1177/1352458514565959. Epub 2015 Jan 26.

Home-based training to improve manual dexterity in patients with multiple sclerosis: A randomized controlled trial

Christian P Kamm¹, Heinrich P Mattle², René M Müri³, Mirjam R Heldner², Verena Blatter², Sandrine Bartlome³, Judith Lüthy³, Debora Imboden³, Giovanna Pedrazzini², Stephan Bohlhalter⁴, Roger Hilfiker⁵, Tim Vanbellinghen⁶



Raghavan & Kapila

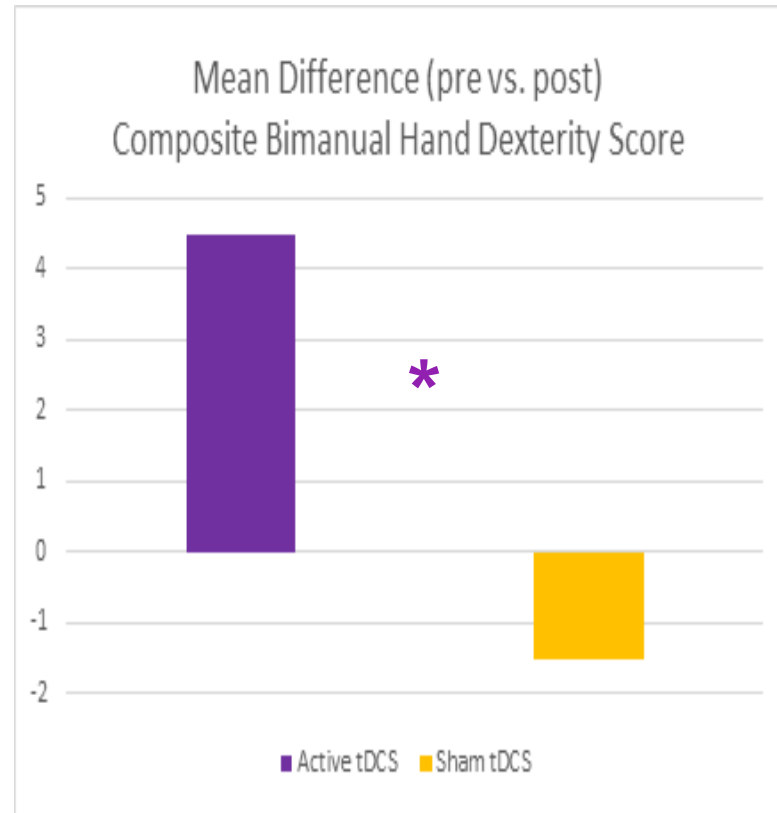


Primary Outcome:
Instrumented grip
device

Preliminary Results:

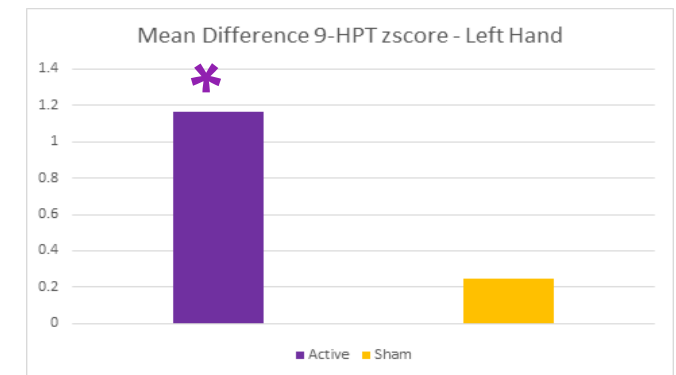
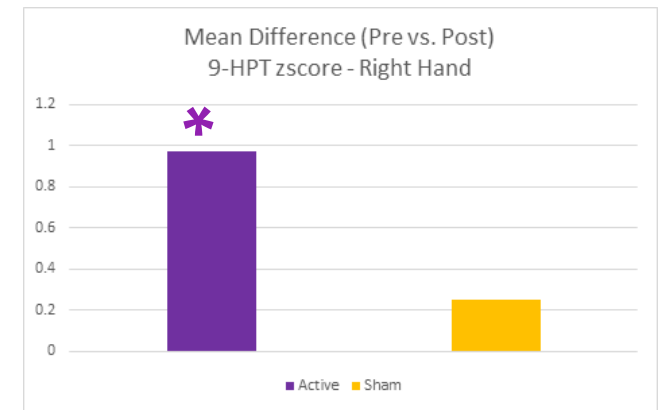
Clinical Manual Dexterity Outcomes (secondary)

Manual dexterity improved in active vs. sham tDCS



9-HPT, MPUT

Change in 9-HPT performance:
By affected hand



Goal: Level A Evidence to Guide Clinical Use in MS

- At-home tDCS is both possible and necessary to reach our participants
- RS-tDCS is a validated protocol to extend lab standards for tDCS RCTs
- A broad range of patients can participate in RS-tDCS
- RS-tDCS demonstrated advantages for Class I/II RCT design
 - Recruiting adequate sample sizes
 - Faster rate of study completion
 - n=120 in 22 months, n=66 in 30 months- including during COVID-19
 - Repeated daily sessions for evaluation of cumulative benefit and define parameters
 - High fidelity to treatment
 - 92% completion rate in 30 session protocol, 98% completion rate 20 session protocol

Summary: Towards tDCS Telehealth in MS care

- People living with MS have many unmet treatment needs
- tDCS- and other noninvasive brain stimulation therapies- offer much promise:
 - Recovery of cognitive or motor functioning
 - “Invisible symptoms”: Distress, Depression, Pain
- At-home tDCS is both possible and necessary to reach our MS participants
 - RS-tDCS is feasible, safe and well-tolerated for most
 - Highly accessible for enrolling a highly diverse range of patients
 - Allows for extended repeated sessions for optimal evaluation
- Preliminary RCT findings - tDCS may be used to “boost” cognitive and motor recovery
- More research is needed
 - Including optimization of “dosing” and maintenance of benefit



tDCS Team

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Pam Best

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Wenni Fan

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Robert Charlson, MD

Lauren Krupp, MD



<https://med.nyu.edu/research/charvet-lab/>



[@NYUNeuromod](https://twitter.com/NYUNeuromod)



National Institutes of Health
Office of Disease Prevention



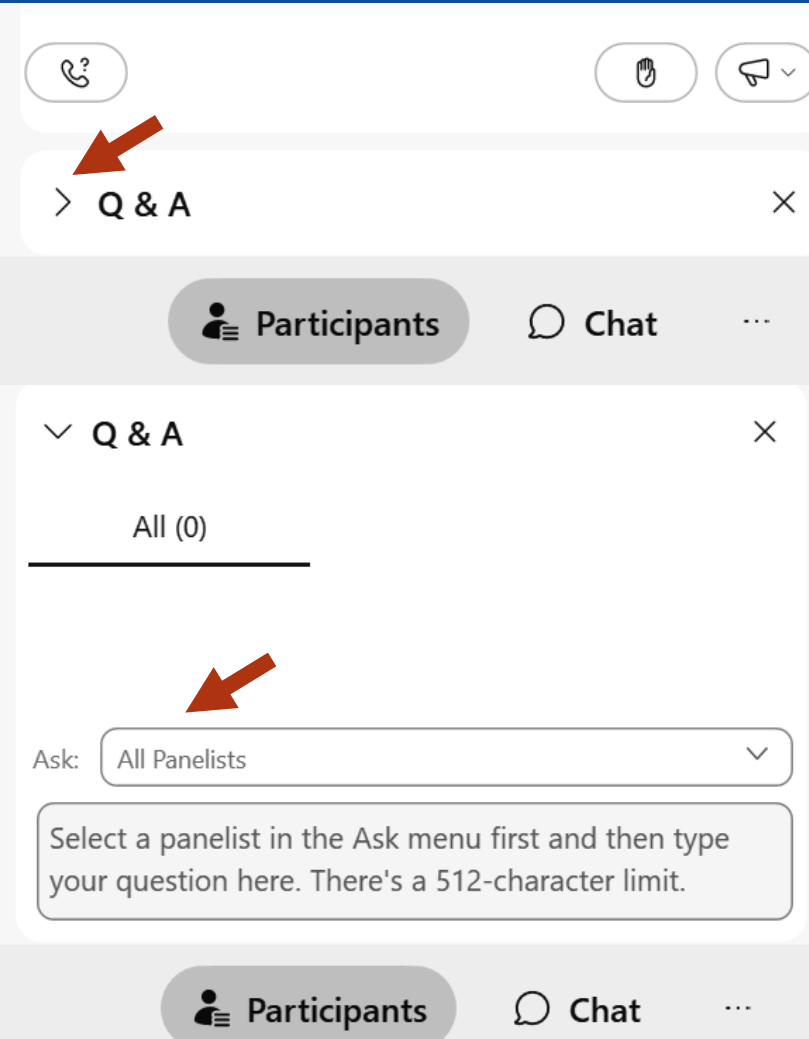
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Q & A Session

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Q & A pod directed to All Panelists

You may use the Chat pod for general commentary or to
request technical assistance





National Institutes of Health
Office of Disease Prevention



Office of Disease Prevention
Putting Prevention Research First

Prevention SIG Webinar Series

Save The Date!

Wednesday, January 26, 2022, 3:00 PM ET

“Update 2022: COVID-19, Multisystem Inflammatory Syndrome in Children, and the Heart”



Presented by

Jane W. Newburger, M.D., M.P.H.

Associate Cardiologist-in-Chief for Academic Affairs, Department of Cardiology, Boston Children’s Hospital;
Commonwealth Professor of Pediatrics, Harvard Medical School



Dongngan Truong, M.D., M.S.

Associate Professor of Pediatrics, Division of Pediatric Cardiology, University of Utah and Primary Children’s Hospital

Introduction by Victoria Pemberton, R.N.C., M.S., C.C.R.C., Program Officer, NHLBI



Thank You!



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