Transcranial Direct Current Stimulation in Pediatric Acquired Brain Injury

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Learning Objectives

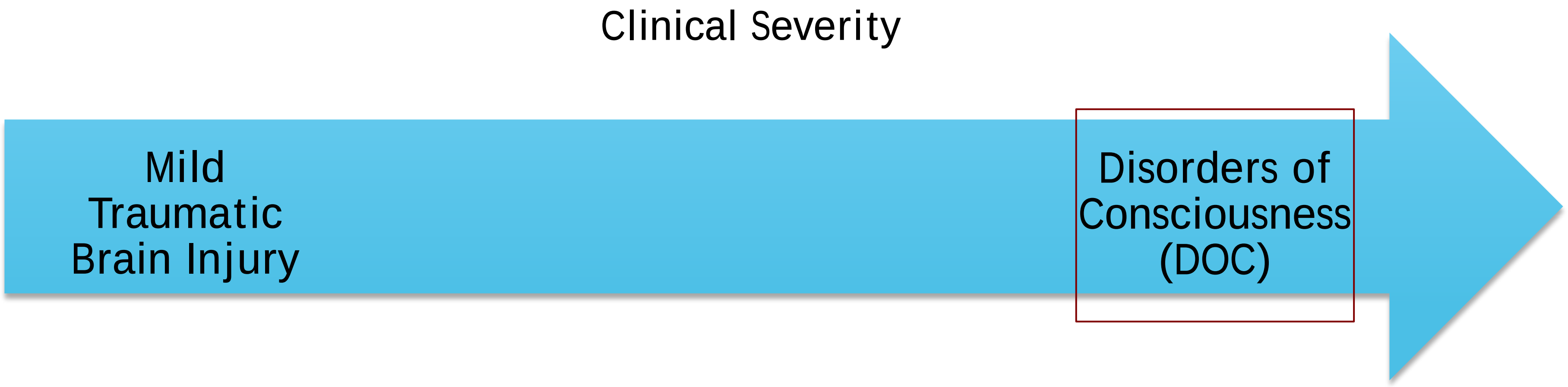
- Define transcranial direct current stimulation (tDCS) and its workings to modulate neuroplasticity in the neurological population
- Using the scientific evidence, explain the efficacy of tDCS in adult Neurorehabilitation with emphasis on DOC
- Discuss the safety/tolerability/feasibility of tDCS in pediatric DOC

Outline

- Introduction to Acquired Brain Injury (ABI)
- Introduction to transcranial direct current stimulation (tDCS)
- tDCS safety and efficacy in Neurorehabilitation
- tDCS in Adult Disorders of Consciousness (DOC)
- tDCS considerations in Pediatric DOC

Acquired Brain Injury (ABI)

- Traumatic and Non-Traumatic Brain Injury
- Leading cause of death and disability in youth in the United States



Disorders of Consciousness (DOC)

- Coma
- Unresponsiveness Wakefulness Syndrome★
- Minimally Conscious State★
- Considerations:

  -Diagnosis and Prognosis

  -Neurorehabilitative therapies

  -Non-invasive brain stimulation

Non-invasive brain stimulation

- Transcranial Magnetic Stimulation
  - “neuro-stimulator”

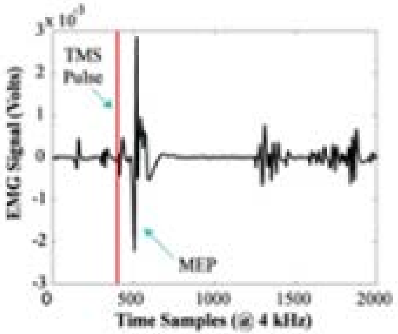
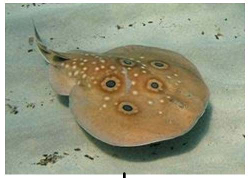


Figure from social and cognitive sciences lab, Universita Di Roma

- Transcranial Direct Current Stimulation
  - “neuro-modulator”

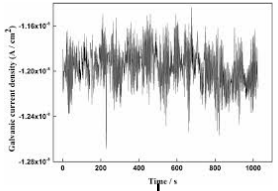
Transcranial Direct Current Stimulation (tDCS)

- Historical Background (Priori, 2003)



Early 1500s

Largus

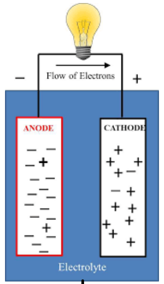


Late 1700s

Galvani

Mid 1900s

Cerletti



Late 1900s

Lippold & Redfearn

2001

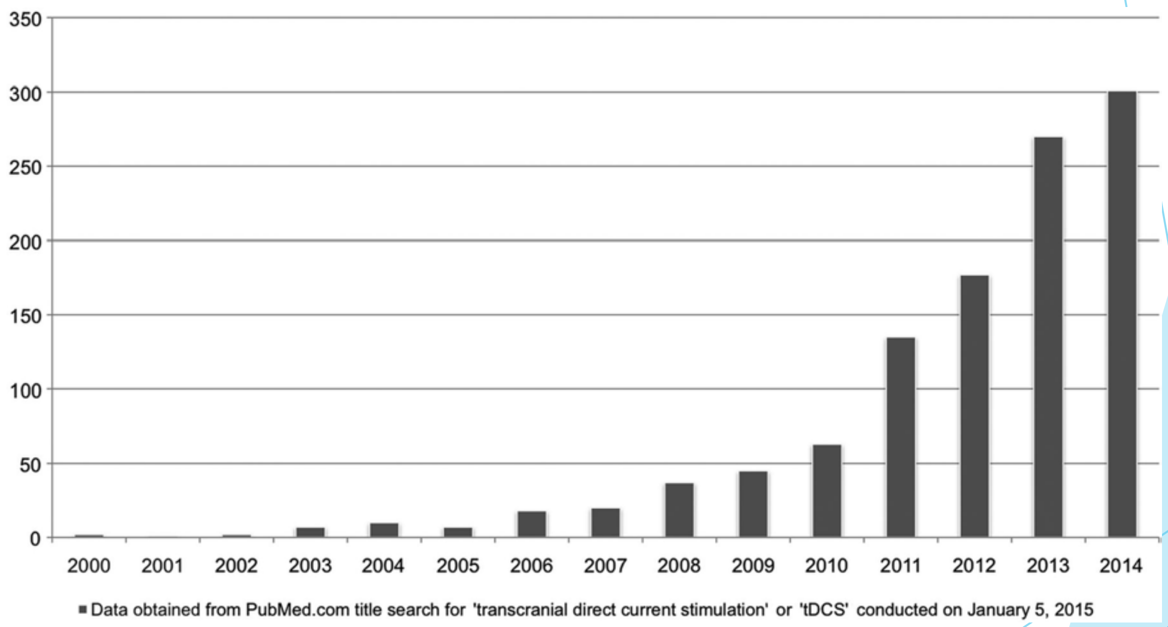
Nitsche & Paulus

tDCS Popularity: Historical Perspective

- PubMed Search with "tDCS" phrase (Thair, 2017)

  -65 articles between 2000-2005

  -1500 articles between 2011-2015



What is tDCS?

- Non-invasive, neuromodulatory brain stimulation
- Low-level direct current for an extended time

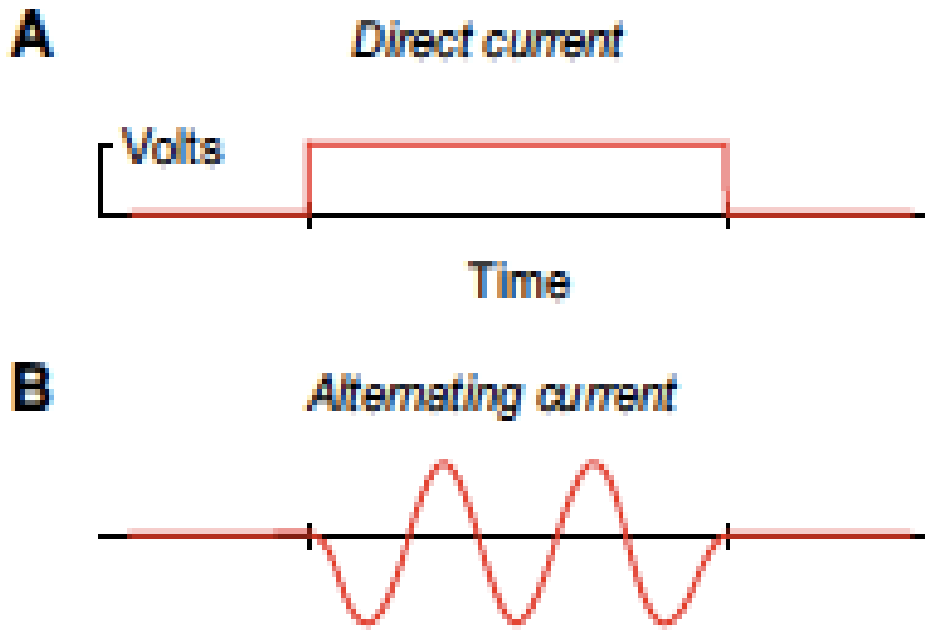


Figure from Reinhart et al. 2017

How does tDCS work?

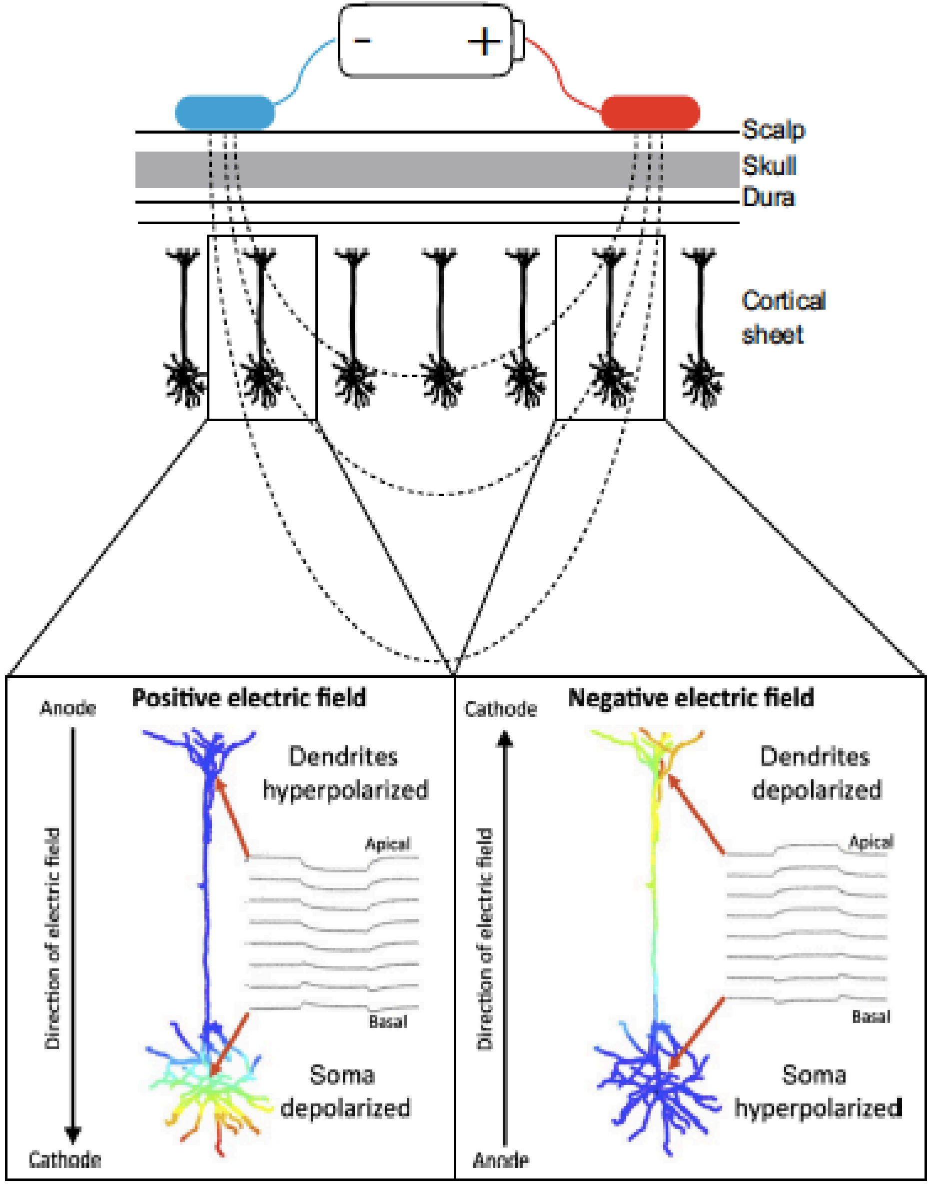


Figure from Reinhart et al. 2017

tDCS set-up

- Conventional tDCS:

Figure from (http://soterixmedical.com/research/1x1)

tDCS Parameters

- Montage (anodal vs. cathodal)
- Current Intensity
- Duration of Stimulation
- Electrode Size
- Electrode Placement
- Saline Solution

(Nitsche et al. 2008)

Electrode Placement

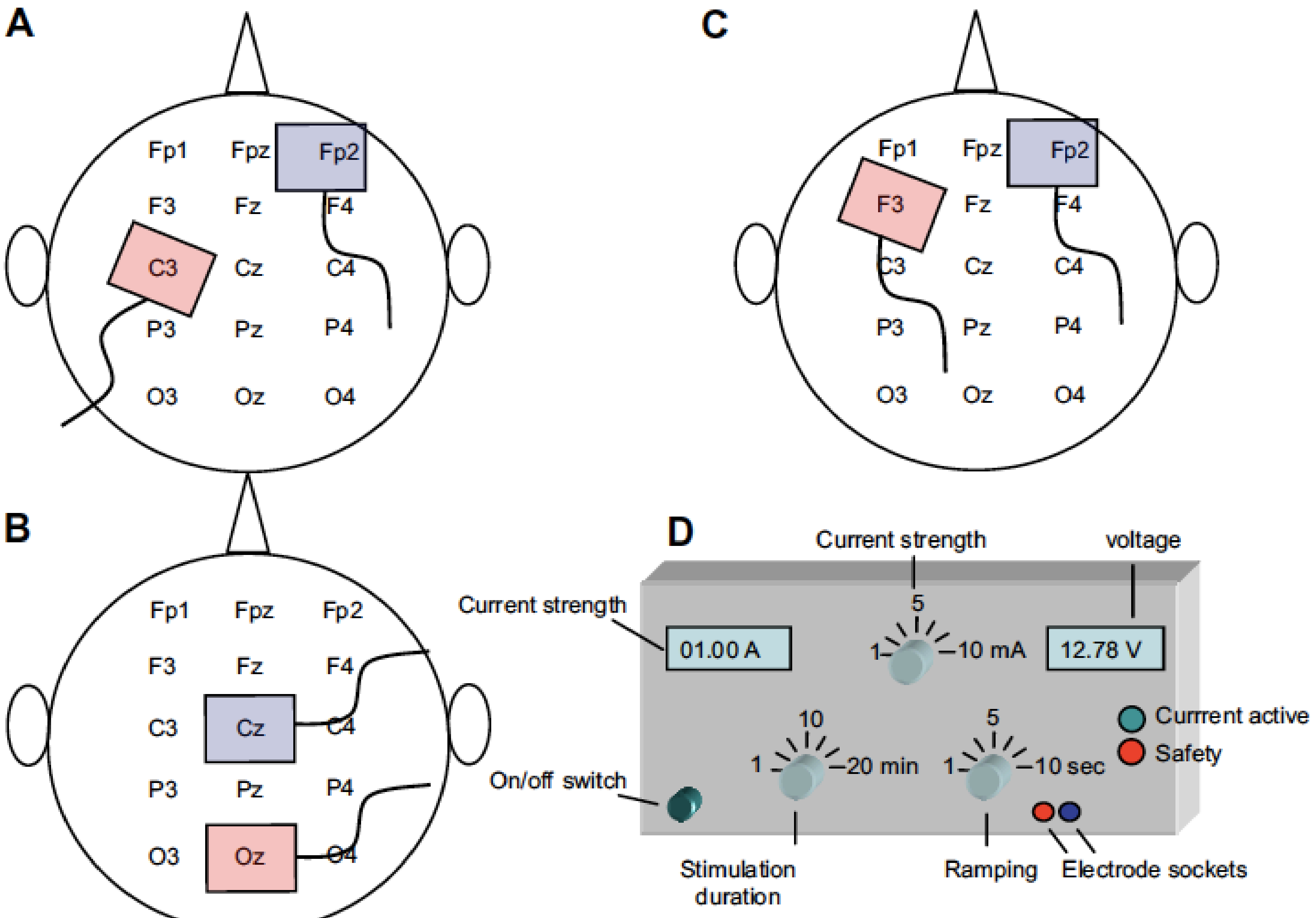


Figure from Nitsche et al. 2008

Do tDCS after-effects last?

- Repetitive stimulation
- Concurrent therapy
- Task and baseline cortical activity

(Nitsche, 2008; Fregni, personal communication)

Why tDCS?

- Easy application, low-cost, and a portable set-up (Wagner et al. 2007)
- Reliable sham application (Nitsche, 2008)
- Neuroplasticity effects (Bolognini et al. 2009)
- Current neurorehabilitative therapies (Bolognini et al. & Page et al. 2015)

tDCS in Neurorehabilitation

- tDCS safety and effectiveness in adults with neurological disorders
- tDCS safety and effectiveness in pediatric neuropsychiatric and neuromotor disorders
- tDCS safety and effectiveness in adults with DOC
- Potential for tDCS in pediatric DOC

tDCS Safety in Adults with Neurological Disorders

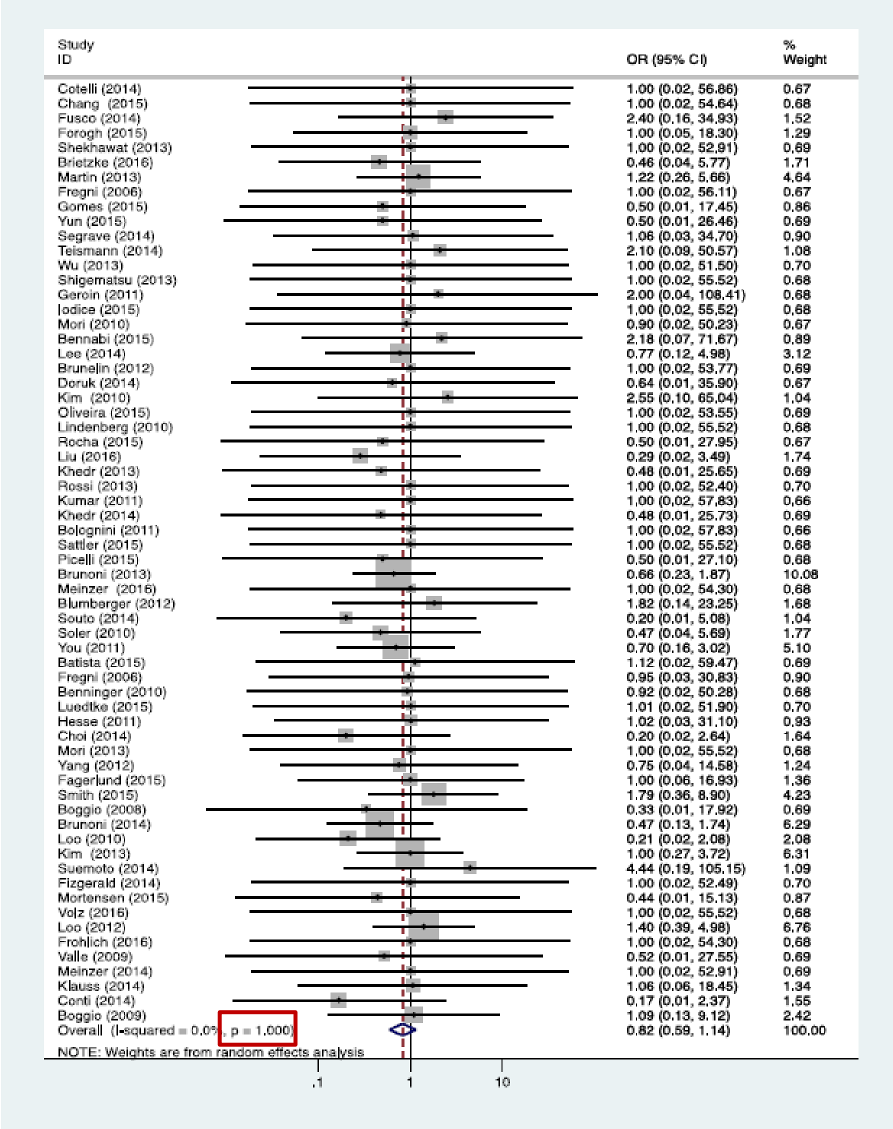


Figure from Aparicio et al. 2016

tDCS Safety in Adults with Stroke (Anodal and Cathodal tDCS)

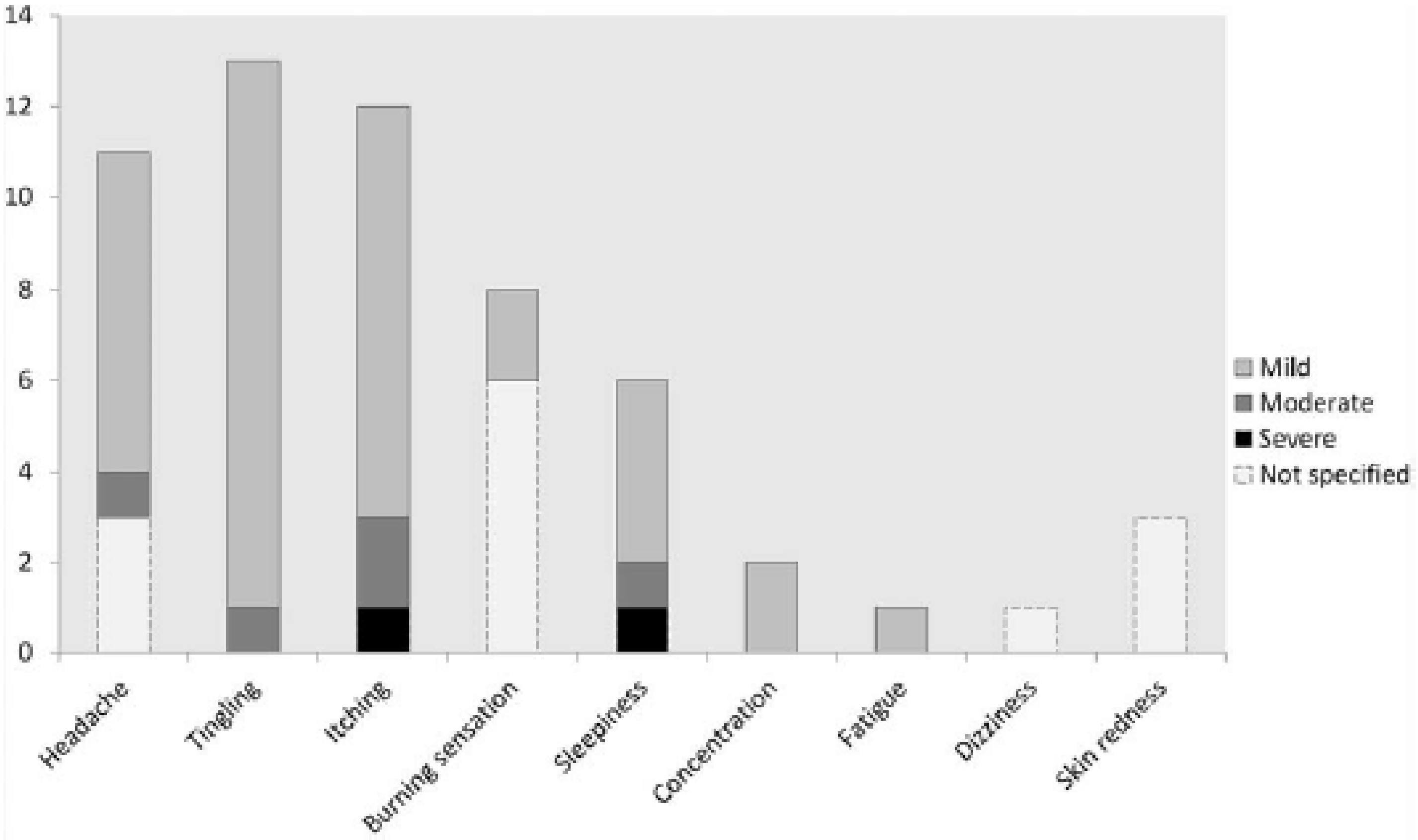


Figure from Russo et al. 2016

tDCS Safety in Adults with Epilepsy

- Most effectiveness studies used cathodal stimulation
- Anodal Stimulation over left DLPFC, 2 mA for 20 minutes for 5 days, in 37 adults with stable (seizure-free 2 months prior to enrollment) temporal-lobe epilepsy (Liu et al. 2016)

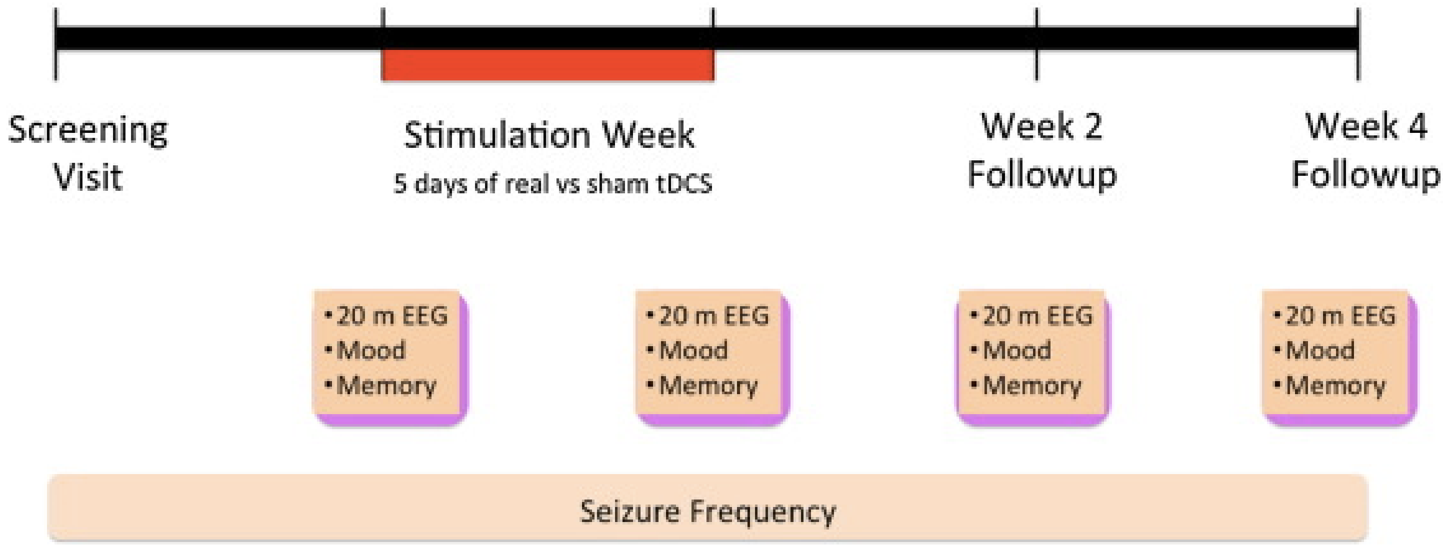


Figure from Liu et al. 2016

tDCS Safety in Adults with Neuropsychiatric and Neuromotor disorders

To date, based on over a total 33,000 sessions and over 1000 subjects who received repeated tDCS sessions, there is no evidence for irreversible injury produced by conventional tDCS protocols within a wide range of stimulation parameters (≤40 min, ≤4 mA, ≤7.2 C).

Bikson et al., 2016

tDCS Common Adverse Effects in Adults

- Anodal Stimulation to Dorsolateral Prefrontal Cortex (DLPFC)
- 209 Experiments with human subjects:

  -Itching

  -Tingling

  -Headache

  -Burning sensation

  -Discomfort

tDCS Effectiveness in Neurological Disorders

- Improvements:
  - Motor learning (Kang et al. 2015)
  - Mobility (Li et al. 2018)
  - Activities of Daily Living (ADLs) (Elsner et al. 2016)
  - Upper limb motor recovery (Butler et al. 2013)

Emerging tDCS Applications in Adult Disorders of Consciousness (DOC)

tDCS Effectiveness in Adult DOC

- Thibaut et al. 2014
- 1 Anodal tDCS (LDLPFC) and 1 Sham session
- VS/UWS (n = 25 adults), MCS (n = 30 adults)
- > 1-week onset; Free of sedatives and neurostimulants
- Findings: CRS-R: Significant treatment effects in MCS (*p* = 0.003)

  Non-significant in VS/UWS (p = 0.952)

  Clinical improvement in CRS-R subscales (13 MCS and 2 VS)

  At 12 months: No Retention

tDCS Effectiveness in Adult DOC

- Estraneo et al. 2017
- 5 consecutive Anodal (LDLPFC) tDCS and 5 consecutive Sham sessions
- VS/UWS (n = 7 adults), MCS (n = 6 adults)
- Onset > 3 months; excluded patients with neurostimulants
- Findings: CRS-R= Post stimulation: Non-significant

  At follow up: 2 patients emerged from MCS and 1 VS to MCS+

  EEG = Post stimulation: Non-significant (3 MCS and 2 VS)

tDCS Effectiveness in Adult DOC

- Angelakis et al. 2014
- 1st round: 5 sham, 5 (1) mA, 5 (2) mA Anodal (LDLPFC or LPSMC) tDCS
- 2nd round: 10 consecutive sessions
- VS/UWS (n = 7 adults), MCS (n = 3 adults)
- > 6 month onset; Patients on meds (baclofen, antiepileptic)
- Findings: Post Stimulation: Significant improvement in MCS patients (CRS-R and Neuroimaging)

  6 VS patients no improvement

  1 VS patient changed status to MCS

  2nd round (MCS-) patient emerged to consciousness

tDCS Effectiveness in Adult DOC

- Huang et al. 2017
- 5 consecutive Anodal Posterior Parietal tDCS and 5 Sham sessions
- MCS (n = 37 adults)
- > 1 month onset; Free of sedatives; no CNS active meds
- Findings: CRS-R: Significant treatment effects at day 5 (p = 0.012)

  No significant effect at day 10 (p = 0.135)

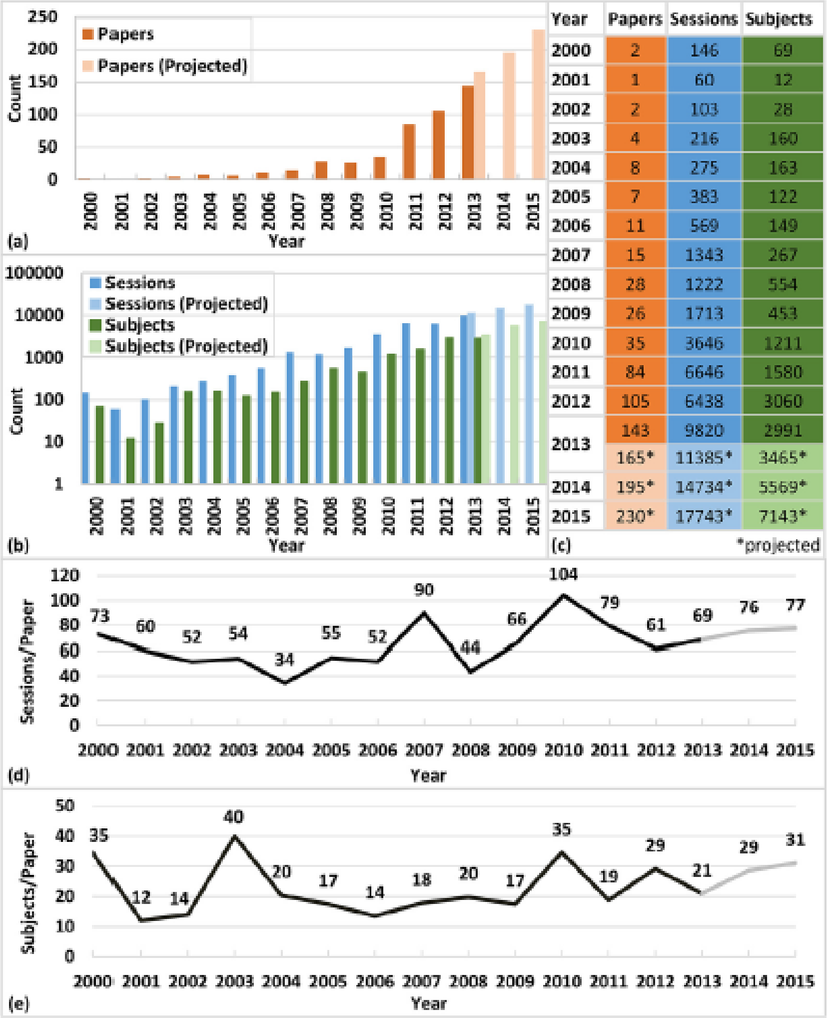
tDCS Effectiveness in Adult DOC

- Cavaliere et al. 2016
- 1 Anodal (DLPFC) tDCS and 1 Sham session
- MCS (n = 19 adults)
- > 28 days onset; Free of sedatives and neurostimulants
- Findings: CRS-R: Improvement in 6 MCS patients

  fMRI: activation of left lateral fronto-parietal cortices in tDCS responders

  Non-responders showed an increased connectivity in midline cortical structures

tDCS Safety in Pediatric Rehabilitation



Year	Papers	Sessions	Subjects
2000	2	146	69
2001	1	60	12
2002	2	103	28
2003	4	216	160
2004	8	275	163
2005	7	383	122
2006	11	569	149
2007	15	1343	267
2008	28	1222	554
2009	26	1713	453
2010	35	3646	1211
2011	84	6646	1580
2012	105	6438	3060
2013	143	9820	2991
	165*	11385*	3465*
2014	195*	14734*	5569*
2015	230*	17743*	7143*

(c) *projected

No adverse events reported in 500 pediatric participants (at least 2800 tDCS sessions) with a variety of neurological diagnoses

Figure from Bikson et al. 2016

tDCS Safety: Pediatric Neuromotor Rehabilitation

Study or Subgroup	Active tDCS Events	Active tDCS Total	Sham Events	Sham Total	Weight	Risk Difference IV, Random, 95% CI
Aree-uea 2014	0	23	1	23	17.3%	-0.04 [-0.16, 0.07]
Bhanpuri 2015	0	9	0	9	6.0%	0.00 [-0.19, 0.19]
Duarte 2014	0	12	0	12	10.0%	0.00 [-0.15, 0.15]
Gillick 2015	1	6	0	6	1.7%	0.17 [-0.19, 0.53]
Grecco 2014 b	0	12	0	12	10.0%	0.00 [-0.15, 0.15]
Grecco 2014 c	0	10	0	10	7.2%	0.00 [-0.17, 0.17]
Grecco 2015	0	10	0	10	7.2%	0.00 [-0.17, 0.17]
Grecco 2017	0	6	0	6	3.0%	0.00 [-0.27, 0.27]
Kirton 2017	0	12	0	12	10.0%	0.00 [-0.15, 0.15]
Lazzari 2017	0	10	0	10	7.2%	0.00 [-0.17, 0.17]
Moura 2017	0	10	0	10	7.2%	0.00 [-0.17, 0.17]
Young 2014	0	14	0	14	13.2%	0.00 [-0.13, 0.13]
Total (95% CI)		**134**		**134**	**100.0%**	**-0.00 [-0.05, 0.04]**
Total events	1		1			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.36$, df = 11 (P = 1.00); $I^2 = 0\%$

Test for overall effect: Z = 0.20 (P = 0.84)

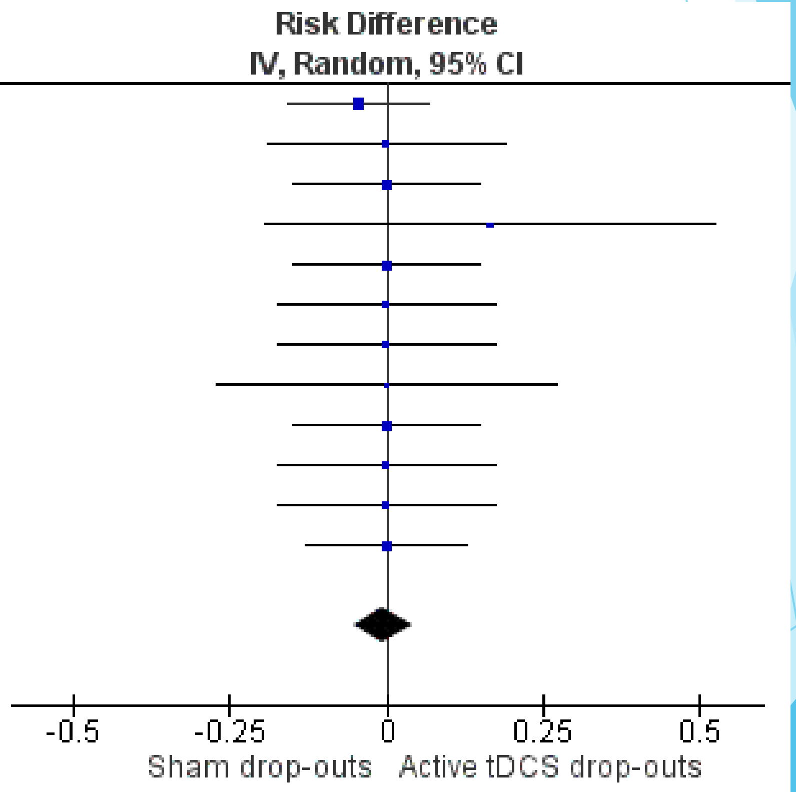


Figure from Saleem et al. (in preparation)

tDCS Safety in Pediatric Epilepsy

- Anodal (posterior temporal area) and Cathodal (parietal area) stimulation, 0.3 to 0.7 mA for 20-40 minutes for 15 sessions, in 18 children (4-8 years) with generalized convulsive fits (Shelyakin et al. 2001)

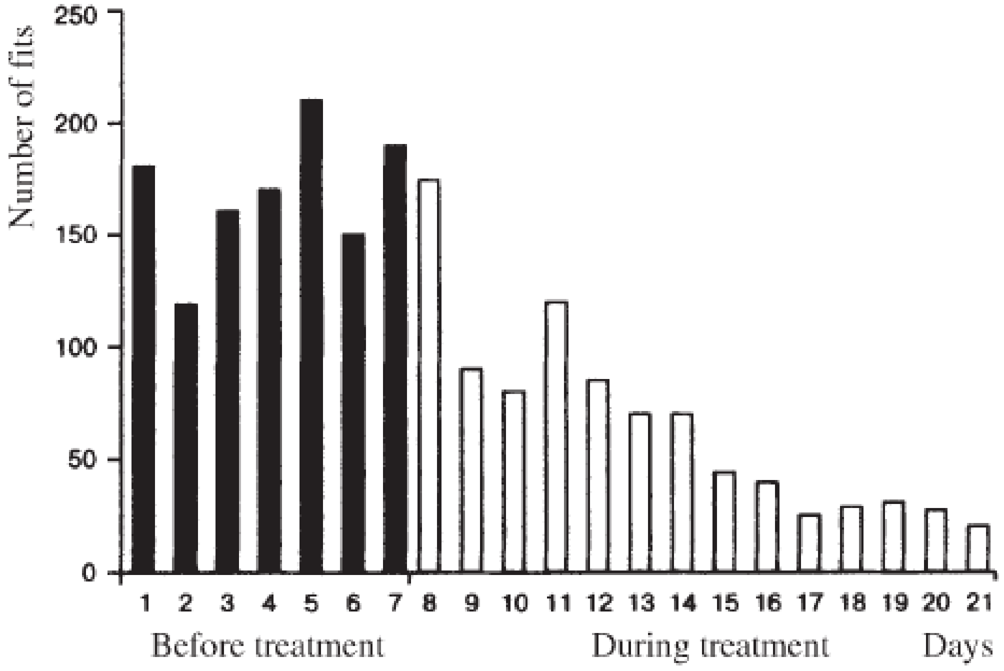
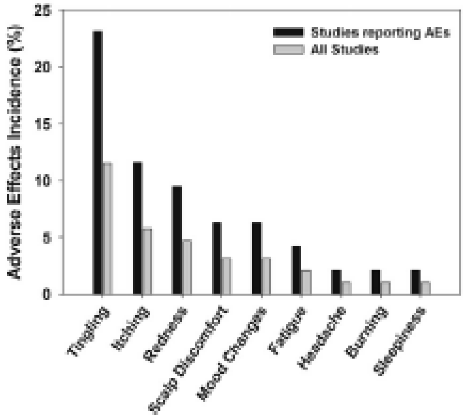


Fig. 3. Histogram showing changes in the numbers of convulsive fits in patient G before and after treatment by transcranial micropolarization.

Figure from Shelyakin et al. 2001

Pediatric Neuromotor Rehabilitation: Adverse Effects

- 191 Participants, 4-18 years old (Krishnan et al.2015)



- Seizure (one letter to the editor) (Ekici, 2015)

"Adverse effects appear to occur at a lower frequency in children and adolescents as compared to adults"

(Ciechanski & Kirton, 2016)

tDCS Effectiveness: Pediatric Neuromotor Rehabilitation

Study or Subgroup	Active tDCS Mean	Active tDCS SD	Active tDCS Total	Sham tDCS Mean	Sham tDCS SD	Sham tDCS Total	Weight	Mean Difference IV, Random, 95% CI
1. Velocity								
Grecco 2014 b	0.9	0.1	12	0.6	0.1	12	43.7%	0.30 [0.22, 0.38]
Grecco 2014 c	1.04	0.21	10	0.8	0.2	10	21.1%	0.24 [0.06, 0.42]
Grecco 2015	0.85	0.11	10	0.7	0.14	10	35.2%	0.15 [0.04, 0.26]
Total (95% CI)			**32**			**32**	**100.0%**	**0.23 [0.13, 0.34]**
Heterogeneity: Tau² = 0.00; Chi² = 4.66, df = 2 (P = 0.10); I² = 57%								
Test for overall effect: Z = 4.48 (P < 0.00001)								
2. Step length								
Grecco 2014 b	0.32	0.08	12	0.34	0.05	12	42.5%	-0.02 [-0.07, 0.03]
Grecco 2014 c	0.4	0.09	10	0.34	0.1	10	24.2%	0.06 [-0.02, 0.14]
Grecco 2015	0.38	0.07	10	0.41	0.08	10	33.3%	-0.03 [-0.10, 0.04]
Total (95% CI)			**32**			**32**	**100.0%**	**-0.00 [-0.05, 0.04]**
Heterogeneity: Tau² = 0.00; Chi² = 3.18, df = 2 (P = 0.20); I² = 37%								
Test for overall effect: Z = 0.16 (P = 0.87)								
3. Stride length								
Grecco 2014 b	0.68	0.14	12	0.65	0.16	12	17.8%	0.03 [-0.09, 0.15]
Grecco 2014 c	0.91	0.07	10	0.79	0.07	10	68.5%	0.12 [0.06, 0.18]
Grecco 2015	0.78	0.18	10	0.71	0.13	10	13.6%	0.07 [-0.07, 0.21]
Total (95% CI)			**32**			**32**	**100.0%**	**0.10 [0.05, 0.15]**
Heterogeneity: Tau² = 0.00; Chi² = 1.88, df = 2 (P = 0.39); I² = 0%								
Test for overall effect: Z = 3.75 (P = 0.0002)								
4. Step width								
Grecco 2014 b	0.17	0.09	12	0.16	0.01	12	28.1%	0.01 [-0.04, 0.06]
Grecco 2014 c	0.16	0.02	10	0.16	0.11	10	15.4%	0.00 [-0.07, 0.07]
Grecco 2015	0.17	0.03	10	0.18	0.05	10	56.5%	-0.01 [-0.05, 0.03]
Total (95% CI)			**32**			**32**	**100.0%**	**-0.00 [-0.03, 0.02]**
Heterogeneity: Tau² = 0.00; Chi² = 0.40, df = 2 (P = 0.82); I² = 0%								
Test for overall effect: Z = 0.20 (P = 0.84)								

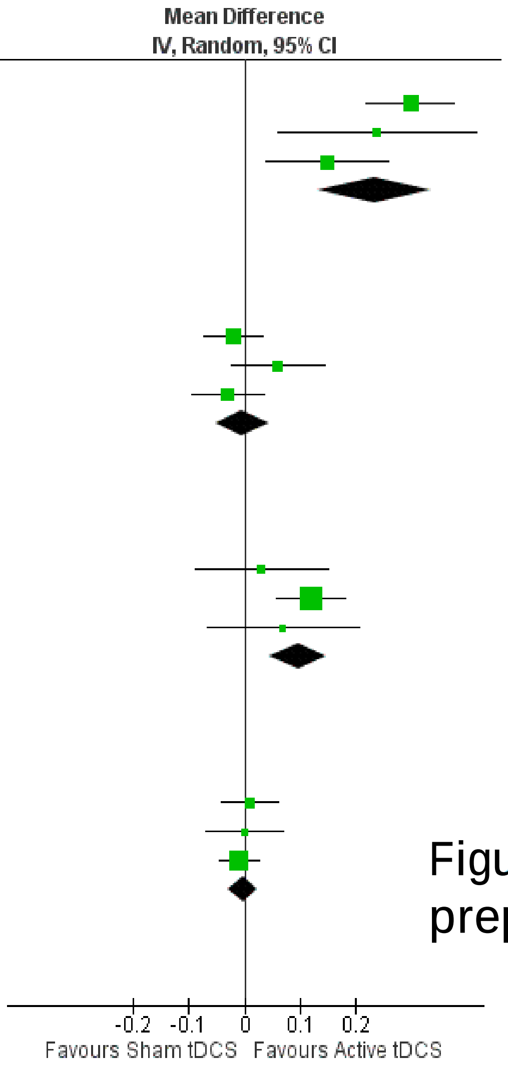


Figure from Saleem et al. (in preparation)

tDCS Effectiveness (at 1 month follow-up): Pediatric Neuromotor Rehabilitation

Study or Subgroup	Active tDCS Mean	Active tDCS SD	Active tDCS Total	Sham tDCS Mean	Sham tDCS SD	Sham tDCS Total	Weight	Mean Difference IV, Random, 95% CI
1. Velocity								
Grecco 2014 b	0.8	0.1	12	0.5	0.1	12	52.9%	0.30 [0.22, 0.38]
Grecco 2015	0.73	0.15	10	0.64	0.14	10	47.1%	0.09 [-0.04, 0.22]
Total (95% CI)			**22**			**22**	**100.0%**	**0.20 [-0.00, 0.41]**
Heterogeneity: Tau² = 0.02; Chi² = 7.50, df = 1 (P = 0.006); I² = 87%								
Test for overall effect: Z = 1.92 (P = 0.06)								
2. Step length								
Grecco 2014 b	0.36	0.04	12	0.33	0.03	12	51.5%	0.03 [0.00, 0.06]
Grecco 2015	0.26	0.08	10	0.42	0.08	10	48.5%	-0.16 [-0.23, -0.09]
Total (95% CI)			**22**			**22**	**100.0%**	**-0.06 [-0.25, 0.12]**
Heterogeneity: Tau² = 0.02; Chi² = 24.26, df = 1 (P < 0.00001); I² = 96%								
Test for overall effect: Z = 0.65 (P = 0.51)								
3. Stride length								
Grecco 2014 b	0.81	0.11	12	0.79	0.16	12	54.0%	0.02 [-0.09, 0.13]
Grecco 2015	0.71	0.12	10	0.69	0.15	10	46.0%	0.02 [-0.10, 0.14]
Total (95% CI)			**22**			**22**	**100.0%**	**0.02 [-0.06, 0.10]**
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%								
Test for overall effect: Z = 0.49 (P = 0.63)								
4. Step width								
Grecco 2014 b	0.17	0.01	12	0.15	0.08	12	27.1%	0.02 [-0.03, 0.07]
Grecco 2015	0.17	0.02	10	0.18	0.03	10	72.9%	-0.01 [-0.03, 0.01]
Total (95% CI)			**22**			**22**	**100.0%**	**-0.00 [-0.03, 0.02]**
Heterogeneity: Tau² = 0.00; Chi² = 1.34, df = 1 (P = 0.25); I² = 25%								
Test for overall effect: Z = 0.14 (P = 0.89)								

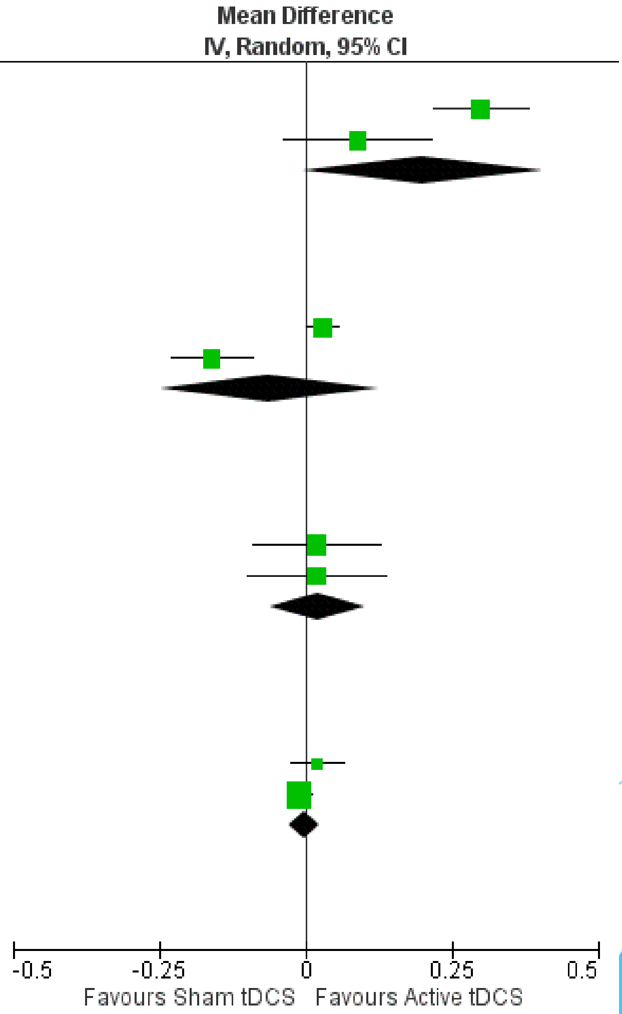


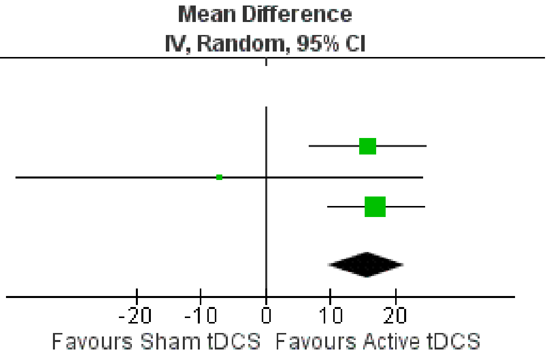
Figure from Saleem et al. (in preparation)

tDCS Effectiveness: Pediatric Neuromotor Rehabilitation

Post-tDCS

Study or Subgroup	Active tDCS Mean	SD	Total	Sham tDCS Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1. Cadence								
Grecco 2014 b	121.6	2.3	12	105.8	15.5	12	40.7%	15.80 [6.93, 24.67]
Grecco 2014 c	98.3	43.4	10	105.3	25.9	10	3.6%	-7.00 [-38.32, 24.32]
Grecco 2015	116.8	8.7	10	99.7	8.2	10	55.7%	17.10 [9.69, 24.51]
Total (95% CI)			**32**			**32**	**100.0%**	**15.70 [9.72, 21.68]**

Heterogeneity: Tau² = 2.42; Chi² = 2.15, df = 2 (P = 0.34); I² = 7%
Test for overall effect: Z = 5.15 (P < 0.00001)



At 1 month follow-up

Study or Subgroup	Active tDCS Mean	SD	Total	Sham tDCS Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1. Cadence								
Grecco 2014 b	118.8	7.1	12	102.1	12.1	12	53.0%	16.70 [8.76, 24.64]
Grecco 2015	101.8	12.4	10	95.8	8.9	10	47.0%	6.00 [-3.46, 15.46]
Total (95% CI)			**22**			**22**	**100.0%**	**11.67 [1.21, 22.14]**

Heterogeneity: Tau² = 37.40; Chi² = 2.88, df = 1 (P = 0.09); I² = 65%
Test for overall effect: Z = 2.19 (P = 0.03)

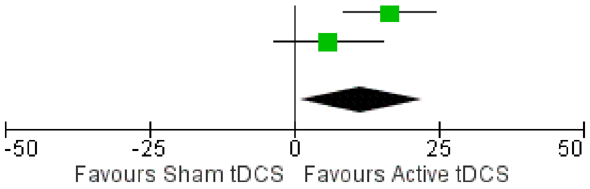


Figure from Saleem et al. (in preparation)

tDCS Effectiveness: Pediatric Neuromotor Rehabilitation

- Qualitative Analysis:

  -Improvements on:

  1) real-world function measures
  2) upper-limb spasticity
  3) hand function

tDCS in Pediatric DOC

tDCS Considerations

- Dosage
  - Current Intensity: Differentially impacts depolarization in children as compared to adults
  - Electrode placement: 10/20 EEG and the TMS-guided method generated different targets
  - Electrode size: 25 cm^2 or 35 cm^2
  - Duration
  - Number of Sessions

tDCS in Pediatric DOC

- tDCS Considerations
  - Electrode Distance
  - Head Size and Current Shunting
  - Sponges
  - Saline Solution Concentration

tDCS in Pediatric DOC

- Considerations for Pediatric DOC Diagnosis
  - Developing brain
  - Compromised anatomy and physiology
  - Seizures
  - Neurostimulant medications

Future Studies in Pediatric Population

- To better understand the physiological effects of tDCS:
  - Response and Predictive Biomarkers
  - Measures that assess the change at the level of functional performance and participation

Upcoming tDCS trial in pediatric DOC

Kennedy Krieger Institute
Brain Injury
Clinical Research Center

- Aims

1) Assess the safety/tolerability/feasibility of anodal stimulation
2) Explore the use of neural correlates and their link to behavioral performance

- Methodology
  - Phase I, single-group, dosage escalation trial
  - 5 Patients with UWS and 5 Patients with MCS at least 1 month post-injury
  - Behavioral Measures to assess safety and feasibility
  - Neurophysiological measures as response and predictive biomarkers

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tDCS in Pediatric Acquired Brain Injury

Thank you!

Questions?