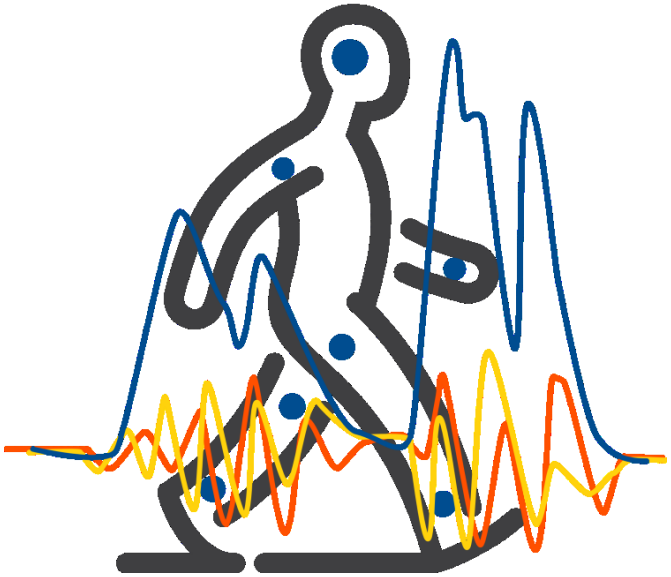
European Reference Network for rare or low prevalence complex diseases
Network Neurological Diseases (ERN-RND)

ean european academy of neurology

European Reference Network for rare or low prevalence complex diseases
Network Neuromuscular Diseases (ERN EURO-NMD)

DG ‚Ataxia and HSP'
3. November 2020

Joint webinar series



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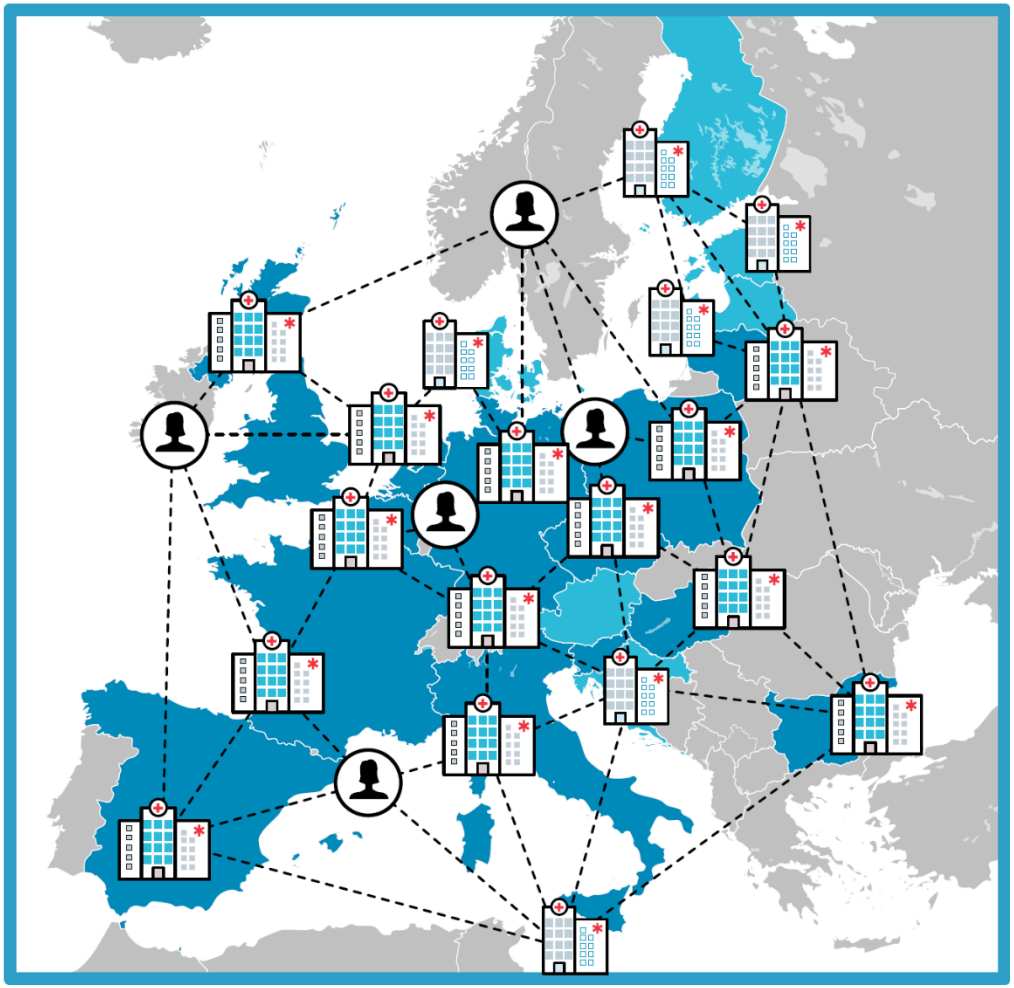
'Non-invasive stimulation for ataxias'

by Bart van de Warrenburg

Radboud University Medical Center, Nijmegen, Netherlands

European Reference Network for RARE Neurological Diseases (ERN-RND)

- **Countries with Full Members**
- **Countries with Affiliated Partners**



ERN-RND covers 6 disease groups:

1. Ataxia and HSP
2. Leukodystrophies
3. Dystonias /NBIA/Paroxysmal disorders
4. Chorea and HD
5. FTD
6. Atypical Parkinsonism

General information about the webinars

- Focus on : RARE neurological, neuromuscular and movement disorders and **neurorehabilitation**
- 40-45min presentation
- 15min Q&A session at the end (please write your questions in the Q&A)
- Recorded Webinar and presentation to be found at the latest 2 weeks after on: http://www.ern-rnd.eu/education-training/past-webinars/
- Further information: http://www.ern-rnd.eu/disease-knowledge-hub/ataxia/
- Post-webinar survey (2-3min): satisfaction, topic/speaker ideas for next webinars

ePAG: european Patient Advocacy Groups

Mary Kearney

Friedreich's Ataxia Research Alliance Ireland (FARA)
In ERN-RND Patient Advocate for: **Ataxia/HSP**

Speaker: Bart van de Warrenbourg

Training: MD Radboud University Medical Centre (RUMC) in Nijmegen, the Netherlands and honorary fellow for movement disorders at Queen Square, London, UK; PhD obtained in 2005

Current position: Faculty neurologist, associate professor and PI at the Department of Neurology and Donders Institute of the RUMC

Other key positions/activities:

- October 2019: visiting Professor at the UKM Medical Centre in Kuala Lumpur, Malaysia
- Founder and current director of the RUMC Expert Centre for Rare and Genetic Movement Disorders
- Member of various international research consortia, committees, and taskforces in the domain of ataxias and other movement disorders.
- Medical advisor of various patient organizations and has initiated or contributed to various guidelines and standards of care.

Research focus:

- Translational research on rare and genetic movement disorders, in particular cerebellar ataxia: use of molecular genetic and neuroimaging approaches to identify mechanisms that serve as targets for therapeutic interventions (neuromodulation, training, genetic modification)

- Published over 250 papers and various book chapters. His current H-index is 44.

Learning objectives

By the end of this webinar on *non-invasive cerebellar stimulation for ataxias* you will:

- know the various non-invasive stimulation techniques
- be able to weigh the current scientific evidence
- understand current challenges and questions
- start thinking about possible future implementation

Question 1

Non-invasive stimulation for the treatment of ataxias is:

1. Still highly experimental
2. Close to clinical application
3. An established (add-on) to treatment
4. I don’t know

Ataxia treatment

- Exciting, mechanism-based treatment developments
- Still, symptomatic treatment is and will remain necessary
- A major knowledge gap
- Options:
  - drugs (riluzole, valproic acid, thyrotropin-releasing hormone)
  - rehabilitation, exercise, training
  - non-invasive cerebellar stimulation?

Non-invasive cerebellar stimulation

Possible advantages

- Can be widely implemented
- Relatively cheap
- Safe
- Longlasting effects
- Boost effects of other treatment?
- At-home use?

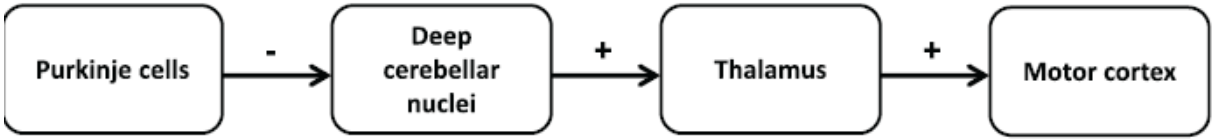
Non-invasive cerebellar stimulation

Current challenges / questions

- Which modality?
- Which protocol?
- Which setting?
- Which patients (etiology, stage)?
- Implementation, equipment, personnel
- Reimbursement?
- Good quality studies!

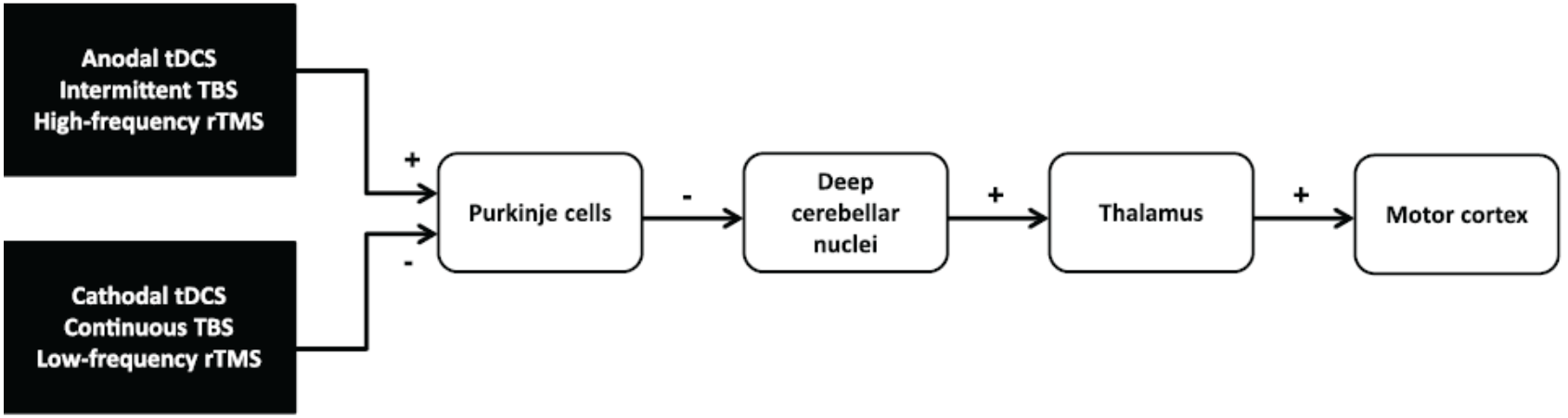
(r)TMS / TBS

tDCS



(r)TMS / TBS

tDCS



(r)TMS / TBS

tDCS

International Journal of
Molecular Sciences

Review

Non-Invasive Cerebellar Stimulation in Neurodegenerative Ataxia: A Literature Review

Alberto Benussi [1], Alvaro Pascual-Leone [2,3] and Barbara Borroni [1,*]

Movement Disorders, Vol. 35, No. 2, 2020

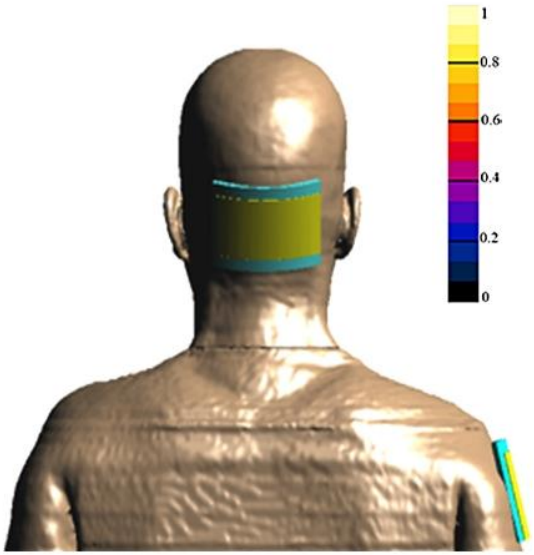
REVIEW

The Role of the Cerebellum in Degenerative Ataxias and Essential Tremor: Insights From Noninvasive Modulation of Cerebellar Activity

Roderick P.P.W.M. Maas, MD,* Rick C.G. Helmich, MD, PhD, and Bart P.C. van de Warrenburg, MD, PhD

Some essentials

- Studies in health controls
- Non-invasive cerebellar stimulation modulates cerebellar activity and connectivity
- Computer modelling; cerebellar brain inhibition (CBI)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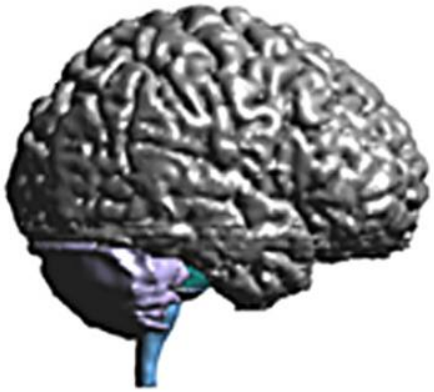
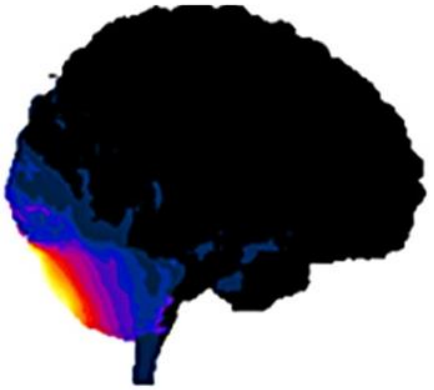
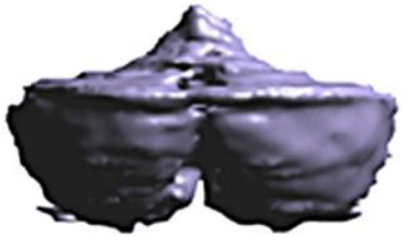
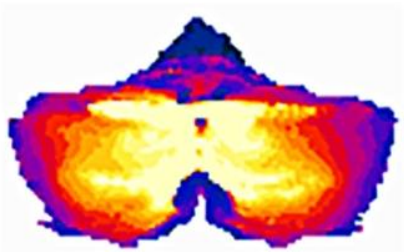
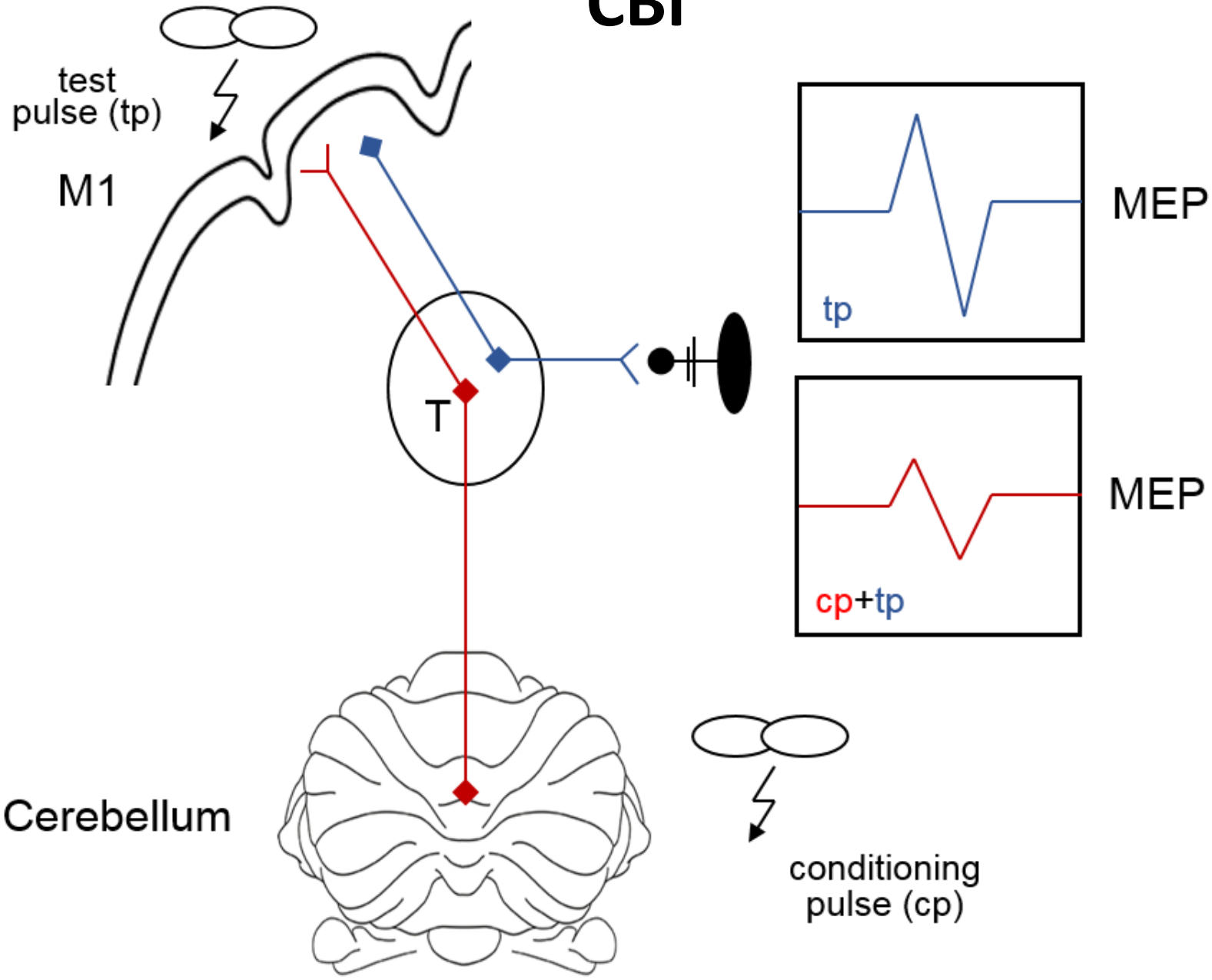








CBI



Some essentials

- Studies in health controls
- Non-invasive cerebellar stimulation modulates cerebellar activity and connectivity
- Computer modelling; cerebellar brain inhibition (CBI)
- Effects on postural control and motor learning
- But – behavioural effects have been inconsistent (mainly tDCS)
- Cumulative effects on *repetitive* stimulation

Repetitive TMS

Table 1. Studies assessing the effects of repetitive transcranial magnetic stimulation (rTMS) in patients with cerebellar ataxia.

Study	Patients	Sham	Blinding	Stimulation	Protocol
[54]	4	No	Not reported	Inion and cerebellar hemispheres	30 pulses (100% MSO) at 0.17 Hz every day for 21 days
[55]	74	Yes	Patients and examiners	Inion and cerebellar hemispheres	30 pulses (100% MSO) at 0.17 Hz every day for 21 days
[56]	20	No	Yes	Inion and cerebellar hemispheres	30 pulses (100% MSO) at 0.2 Hz every day for 8 weeks
[60]	1	No	Not reported	Inion and cerebellar hemispheres	30 pulses (100% MSO) at 0.17 Hz every day for 21 days
[61]	1	Yes	Not reported	Inion and cerebellar hemispheres	500 pulses (90% RMT) at 5 Hz for 10 s with a 50 s interval, every day for 2 days/week for 4 months
[62]	1	Yes	Not reported	Motor cortices and cerebellar hemispheres	40 pulses (100% RMT) over Cz at 0.2 Hz + 20 pulses (50% RMT) over inion at 0.5 Hz every day for 4 weeks
[63]	1	No	Not reported	Inion	1500 pulses (100% MSO) at 10 Hz for 1 s with a 10 s interval, every day for 4 weeks
[64]	20	Yes	Yes	Inion and cerebellar hemispheres	30 pulses (100% MSO) at 0.17 Hz every day for 21 days

MSO: maximum stimulator output; RMT: resting motor threshold.

Benussi, 2020

frontiers in Neurology

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CLINICAL TRIAL
published: 12 February 2019
doi: 10.3389/fneur.2019.00073

Repetitive Transcranial Magnetic Stimulation in Spinocerebellar Ataxia: A Pilot Randomized Controlled Trial

Brad Manor[1,2,3†], *Patricia E. Greenstein*[1,2*†], *Paula Davila-Perez*[1,2], *Seth Wakefield*[1,2], *Junhong Zhou*[2,3] *and Alvaro Pascual-Leone*[1,2,4]

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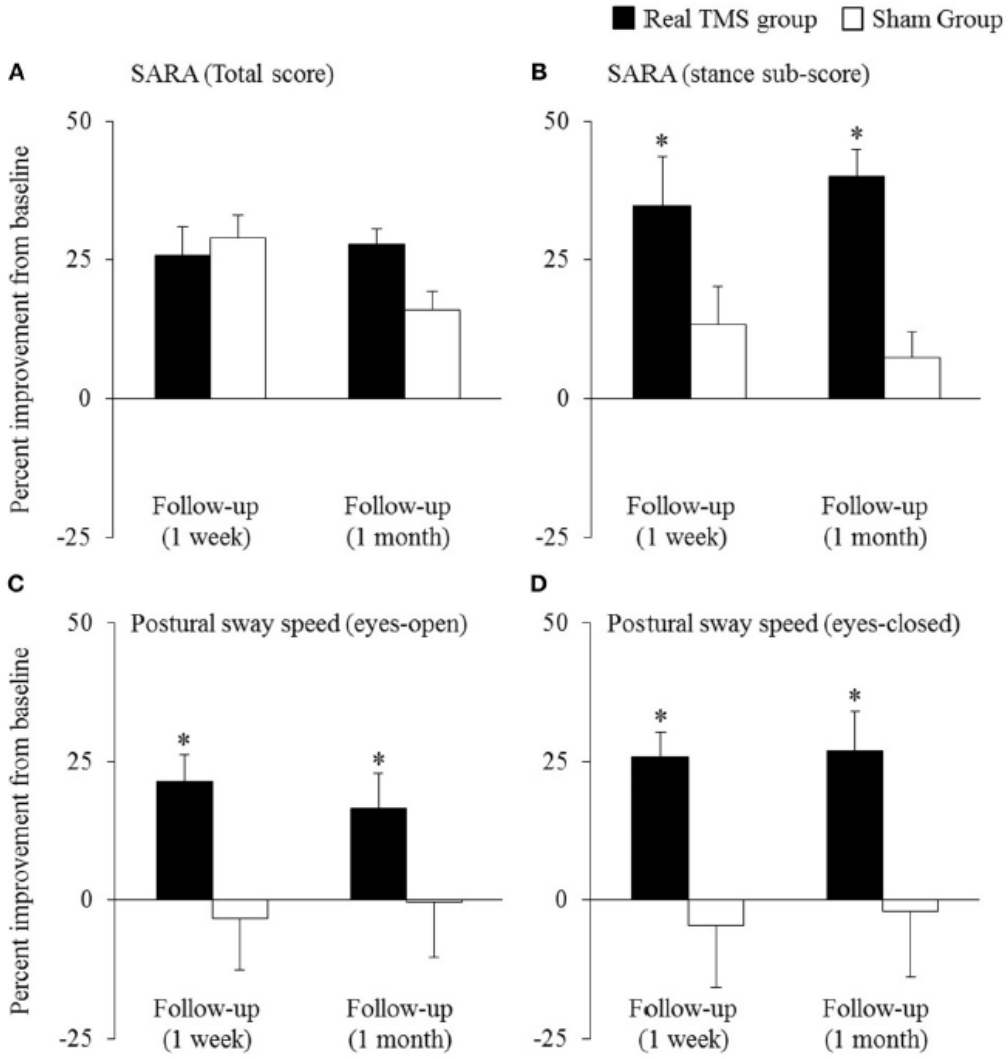
- Double blind, sham-controlled RCT
- 20 SCA patients, mostly SCA3
- MRI-navigated, low-frequency cerebellar rTMS (30 pulses)
- 20 sessions in 4 weeks
- Outcome assessment: immediate and after 1 month
- Primary outcome: SARA
- Secondary outcomes: TUG, 9HPT, posture and gait analyses


Real TMS group
Sham Group
A
SARA (Total score)
B
SARA (stance sub-score)
C
Postural sway speed (eyes-open)
D
Postural sway speed (eyes-closed)
Percent improvement from baseline
50
25
0
-25
*
Follow-up (1 week)
Follow-up (1 month)

	rTMS			Sham		
	Baseline	Follow up (immediate)	Follow-up (1 month)	Baseline	Follow up (immediate)	Follow-up (1 month)
SARA (total)	13.7 ± 2.8	10.7 ± 3.4	9.8 ± 2.6	17.1 ± 4.5	12.9 ± 4.9	14.7 ± 4.0

Safe and well tolerated

No effect on
-TUG
-9HPT
-gait kinematics

tDCS

Table 2. Studies assessing the effects of transcranial direct current stimulation (tDCS) in patients with cerebellar ataxia.

Study	Patients	Sham	Blinding	Anode	Cathode	Protocol
[75]	9	Yes	Patients	Right cerebellar hemisphere	L supraorbital area	1–2 mA, 20 min
[76]	2	Yes	Patients	Right cerebellar hemisphere/left motor cortex	Contralateral supraorbital area	1 mA, 20 min
[78]	3	Yes	Patients and examiners	Motor cortex affected side	Motor cortex unaffected side	2 mA, 20 min for five sessions
[79]	19	Yes	Patients and examiners	Cerebellar hemispheres	Right deltoid muscle	2 mA, 20 min
[81]	20	Yes	Patients and examiners	Cerebellar hemispheres	Right deltoid muscle	2 mA, 20 min for 10 days
[82]	21	Yes	Patients and examiners	Cerebellar hemispheres	Spinal lumbar enlargement	2 mA, 20 min for 10 days
[84]	7	Yes	Patients and examiners	Motor cortices	Contralateral supraorbital area	2 mA, 20 min for five days
[85]	1	No	Not reported	Cerebellar hemispheres	Right shoulder	2.5 mA, 20 min for 60 days
[86]	20	Yes	Patients and examiners	Right cerebellar hemisphere/motor cortex	Right buccinator muscle/contralateral supraorbital region	2 mA, 22 min
[87]	14	Yes	Patients and examiners	Right cerebellar hemisphere/motor cortex	Right buccinator muscle/contralateral supraorbital region	2 mA, 22 min

Benussi, 2020

Movement Disorders, Vol. 30, No. 12, 2015

Cerebellar Transcranial Direct Current Stimulation in Patients With Ataxia: A Double-Blind, Randomized, Sham-Controlled Study

Alberto Benussi, MD,[1] Giacomo Koch, MD,[2,3] Maria Cotelli, MSc,[4] Alessandro Padovani, MD, PhD[1] and Barbara Borroni, MD[1]*

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- Double-blind, sham-controlled RCT
- 19 patients (SCA, FA, AOA2, MSA, FXTAS, ILOCA)
- Cerebellar tDCS, single real or sham session, 2 mA for 20 min
- Outcome assessment: SARA, ICARS, 9HPT, 8MW

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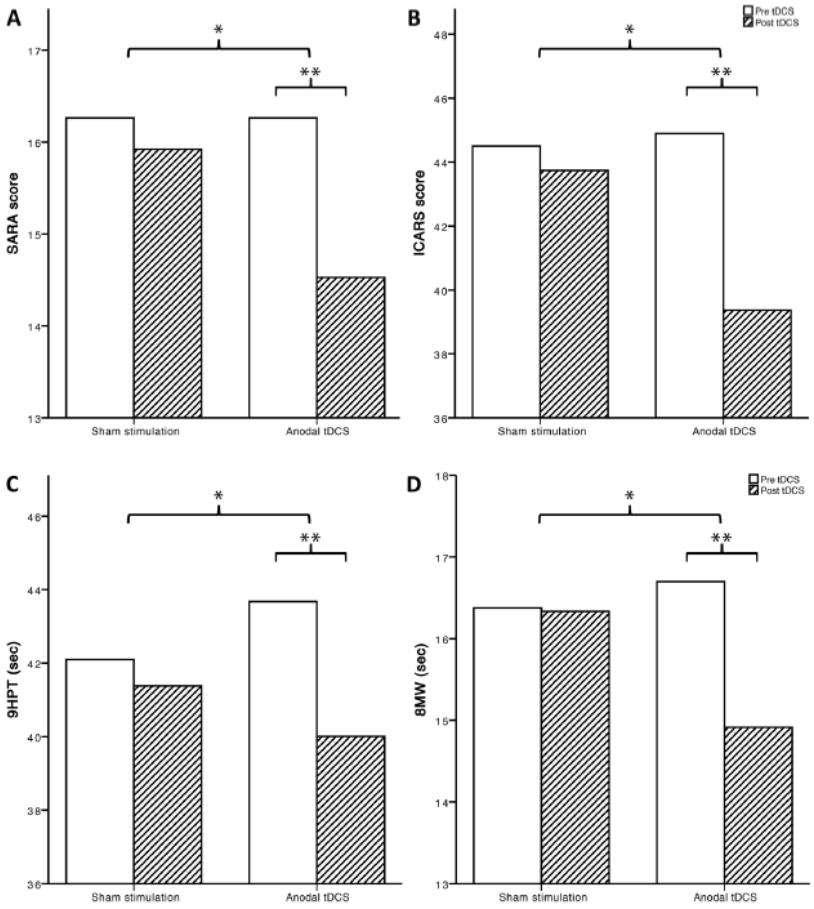

SARA (A), ICARS (B), 9HPT (C), and 8MW (D) scores, pre- and post-sham and anodal tDCS. Values expressed as mean;
ant interaction between type of stimulation (sham stimulation vs. anodal tDCS) and time (pre- vs. post-tDCS);
cant difference between pre- and poststimulation.

Brain Stimulation 10 (2017) 242–250

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

Long term clinical and neurophysiological effects of cerebellar transcranial direct current stimulation in patients with neurodegenerative ataxia

Alberto Benussi [a], Valentina Dell'Era [a], Maria Sofia Cotelli [b], Marinella Turla [b], Carlo Casali [c], Alessandro Padovani [a], Barbara Borroni [a, *]

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- Double-blind, sham-controlled RCT
- 20 ataxia patients (SCA, FA, MSA-C, FXTAS, ILOCA)
- Cerebellar tDCS, 10 sessions/2 weeks, 2 mA for 20 min
- Outcome assessment: at 1 and 3 months
- Clinical outcome measures: SARA, ICARS, 9HPT, 8MW, QoL
- Neurophysiological marker: CBI

Effect on SARA and ICARS

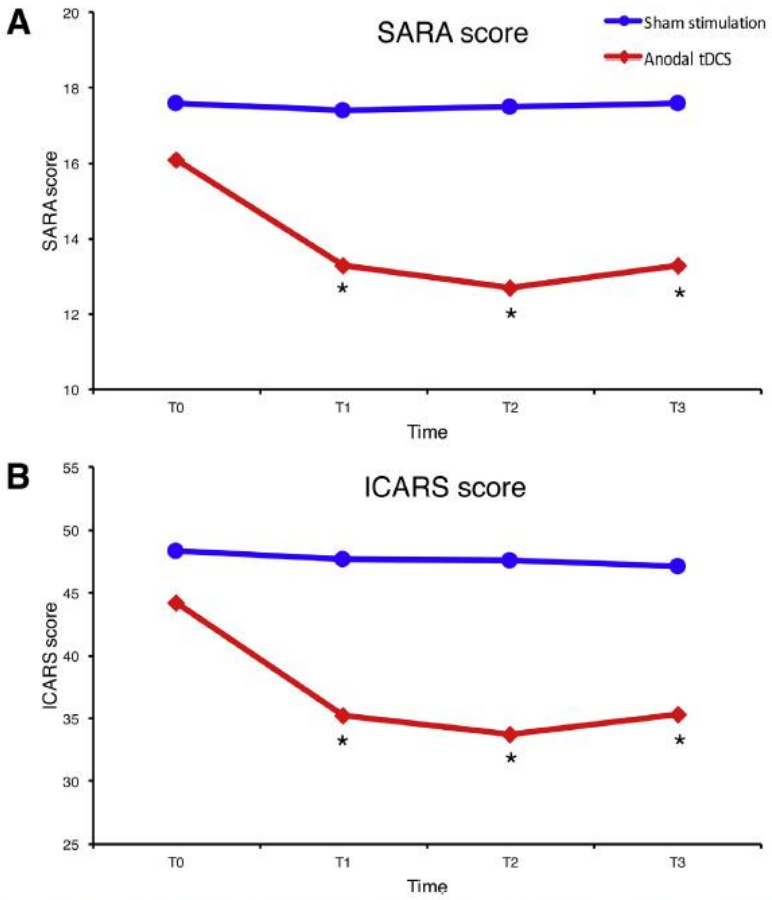
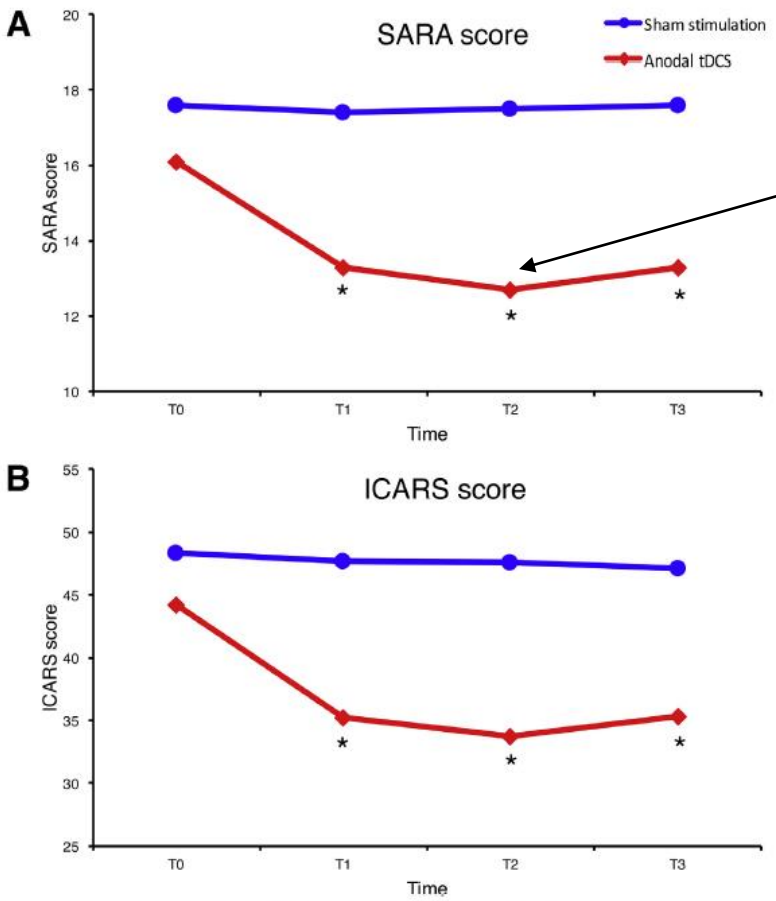


Fig. 2. SARA (A) and ICARS (B) scores, pre- and post-sham and anodal tDCS at different time points (T0: baseline; T1: after 2-weeks' treatment; T2: at 1-month follow-up; T3 at 3-month follow-up); Results are expressed as mean ± standard deviation; *significant difference from baseline (T0).

Effect on SARA and ICARS



SARA -3.48

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Effect on SARA and ICARS

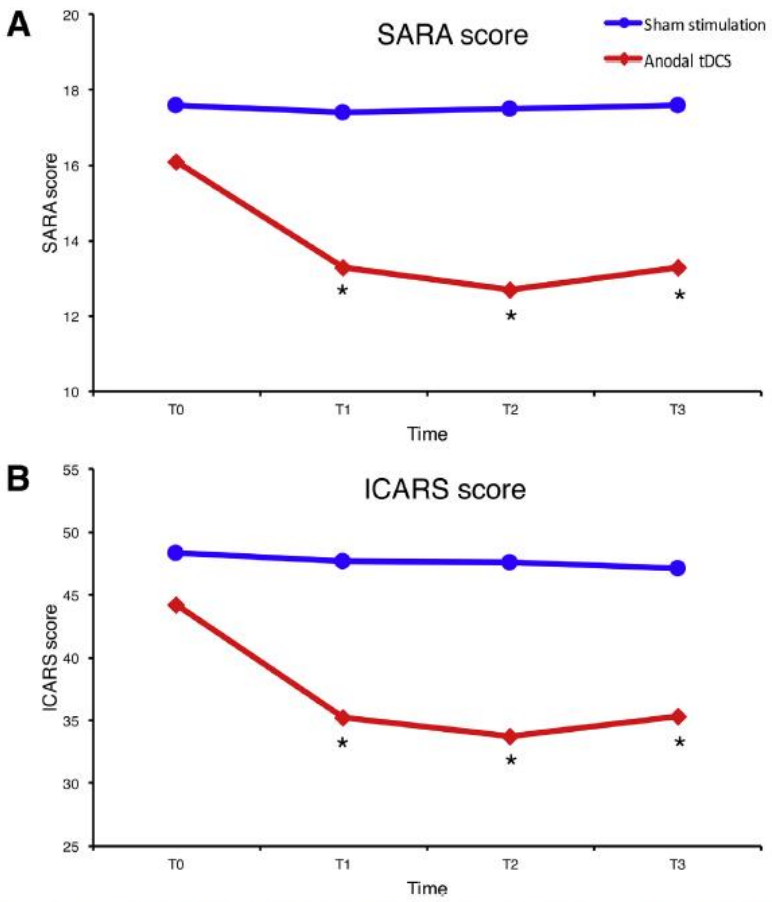
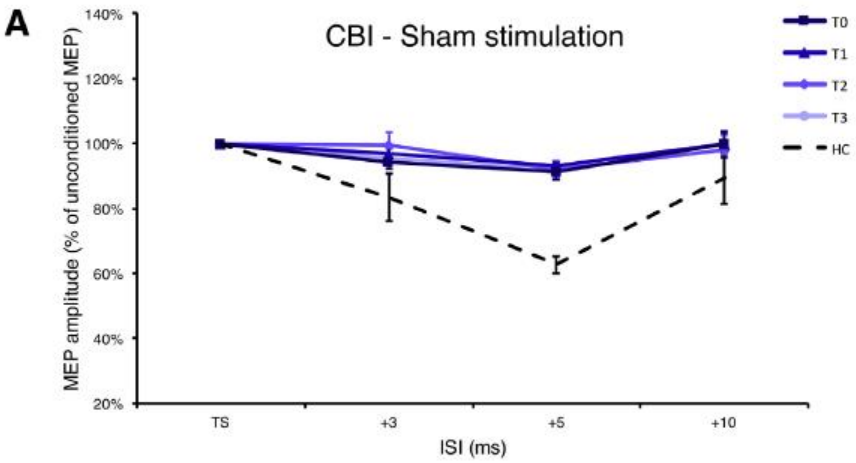


Fig. 2. SARA (A) and ICARS (B) scores, pre- and post-sham and anodal tDCS at different time points (T0: baseline; T1: after 2-weeks' treatment; T2: at 1-month follow-up; T3 at 3-month follow-up); Results are expressed as mean ± standard deviation; *significant difference from baseline (T0).

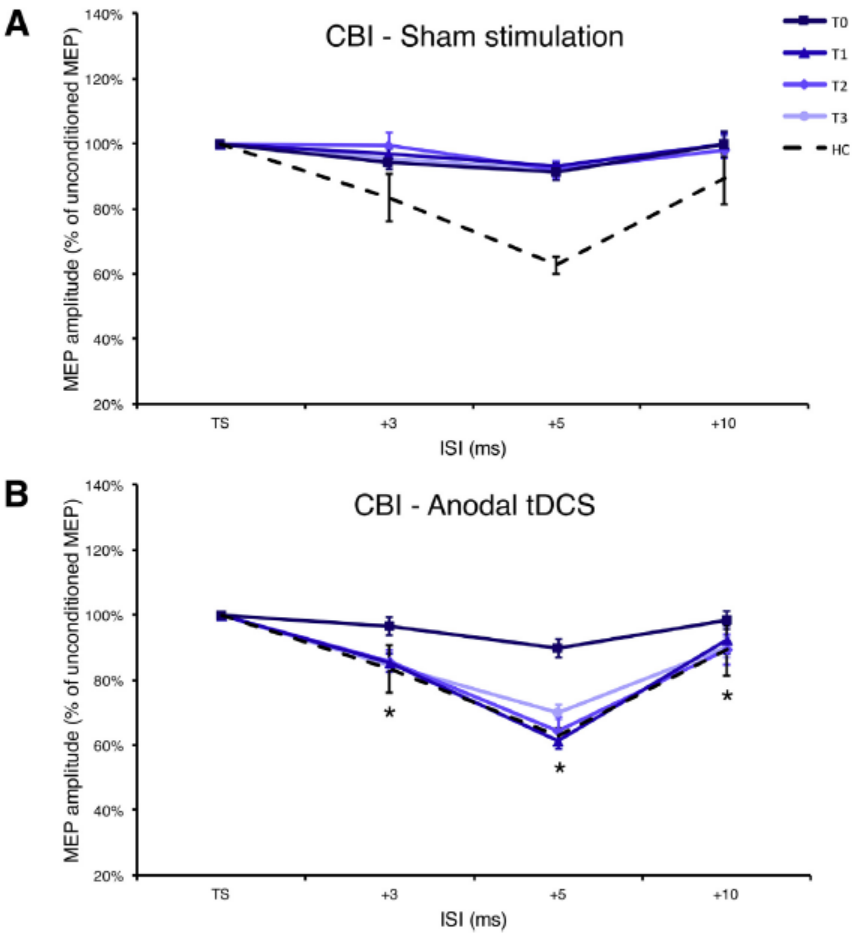
Post hoc:
-similar effects for SCA's vs other etiologies

-better effect in less severly affected patients

Restoration of CBI



Restoration of CBI



Maas *et al. BMC Neurology* (2019) 19:149
https://doi.org/10.1186/s12883-019-1379-2

BMC Neurology

STUDY PROTOCOL Open Access

Cerebellar transcranial direct current stimulation in spinocerebellar ataxia type 3 (SCA3-tDCS): rationale and protocol of a randomized, double-blind, sham-controlled study

Roderick P. P. W. M. Maas[1*], Ivan Toni[2], Jonne Doorduin[1], Thomas Klockgether[3,4], Dennis J. L. G. Schutter[2] and Bart P. C. van de Warrenburg[1]

Maas *et al. BMC Neurology* (2019) 19:149
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- Double-blind, sham-controlled RCT
- 20 SCA3 patients, SARA 3-20, stratification
- Cerebellar tDCS, 10 sessions/2 weeks, 2 mA for 20 min
- Outcome assessment: immediate, and after 3-6-12 months
- Primary outcome: absolute change in SARA after the 10 sessions
- Secondary outcomes: see table

Table 1 Overview of the questionnaires, neurological tests, and kinetic and neurophysiological measurements at the various points in time of the SCA3-tDCS study

	T0 baseline	T0 after tDCS	T1 day 12	T2 3 months	T3 6 months	T4 12 months
Questionnaires						
EQ-5D-5L	X		X	X	X	X
PHQ-9	X		X	X	X	X
POMS 32-item	X		X	X	X	X
iMCQ	X					X
IPAQ parts 1 and 4	X			X		X
FARS part II (ADL)	X		X	X	X	X
Neurological examination						
CCAS scale	X		X	X	X	X
SARA	X	X	X	X	X	X
8MWT	X	X	X	X	X	X
9HPT	X	X	X	X	X	X
PATA repetition	X	X	X	X	X	X
INAS	X		X	X	X	X
Measurements						
TMS	X		X			
Delay EBC	X		X			
Static posturography	X	X	X			

Roderick Maas

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Breaking news

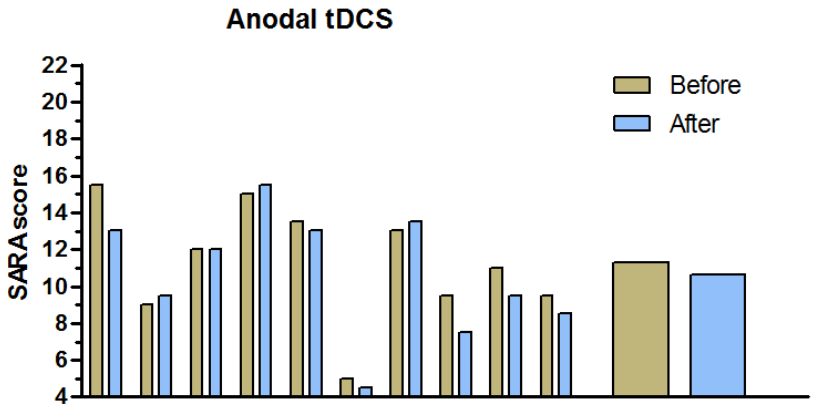
We have the single-session results….

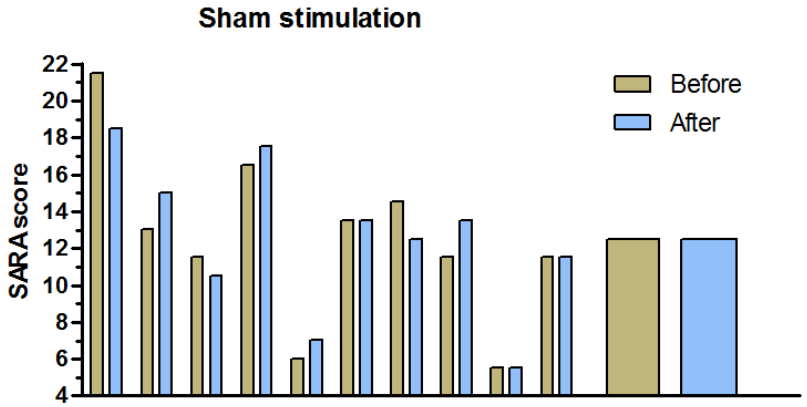
Roderick Maas

Radboudumc

Breaking news

We have the single-session results….





Reasons for negative result

- Repetitive sessions needed (results awaited)
- True lack of effect
- Imperfections of SARA
- Fluctuations of SARA
- Placebo effects
- SCA3-related factors

Evidence so far

- Some moderate to good studies
- Most are small and weak
- Issues with sham and blinding
- Variation in design and stimulation protocols
- Publication bias
- Heterogeneous etiologies
- New studies are being performed!

Question 2

If further evidence of efficacy is provided…

1. I would consider implementing non-invasive stimulation for the treatment of ataxia

2. I would await formal guidelines that comment on non-invasive stimulation for the treatment of ataxia

3. I will never (be able to) implement non-invasive stimulation for the treatment of ataxia

4. I have no opinion yet

Some interesting avenues

- Combining non-invasive stimulation with rehab strategies

Some interesting avenues

- Combining non-invasive stimulation with rehab strategies
- At-home delivery of tDCS

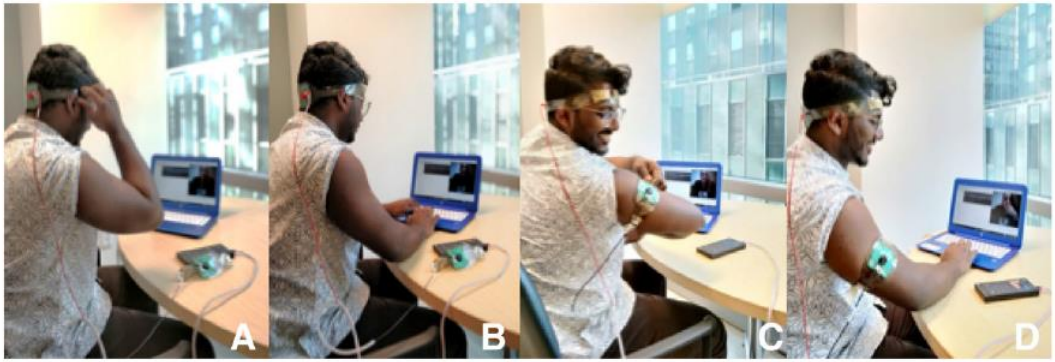


Fig. 1 Example of the RS-tDCS kit and the electrodes preparation and positioning: tDCS headstrap for electrode cerebellar montage with the anode aligned with the median line over the cerebellum and the cathode over the right shoulder; stimulation device; single-use pre-saturated electrodes; laptop. **a** and **b** showed the positioning of the headstrap and the checking of its correct placement by the study technician connected via video conferencing. **c** and **d** showed the positioning of the cathode over the right shoulder and the releasing of the code to unlock the stimulation device for starting the session

Some interesting avenues

- Combining non-invasive stimulation with rehab strategies
- At-home delivery of tDCS
- Targeting non-motor features of cerebellar diseases

frontiers in
PSYCHIATRY

REVIEW ARTICLE
published: 02 April 2014
doi: 10.3389/fpsyt.2014.00033

Restoring cognitive functions using non-invasive brain stimulation techniques in patients with cerebellar disorders

Paul A. Pope* and R. Chris Miall

School of Psychology, University of Birmingham, Birmingham, UK

frontiers in
PSYCHIATRY

REVIEW ARTICLE
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Restoring cognitive functions using non-invasive brain stimulation techniques in patients with cerebellar disorders

Paul A. Pope* and R. Chris Miall

School of Psychology, University of Birmingham, Birmingham, UK

New cerebellar tDCS trial (2021)

RCT in 40 patients

Patients with CCAS

Outcome: neuropsychological tets battery

Hersenstichting

Institutional Logo,
‚Speakers' picture or
disease related picture

Key Points /Conclusions

- Non-invasive cerebellar stimulation is an exciting tool, possibly able to provide symptomatic relief to ataxia patients
- More studies are clearly needed!
- Sham-controlled RCT's, homogeneous cohorts, harmonized protocols/outcomes
- Mechanistic outcomes (neurophysiology, MRI)
- Explore and identify best stimulation protocols (including follow-up sessions)
- Combined interventions (non-invasive stimulation + rehab)
- Investigate effects on non-motor symptoms

Radboudumc

Thank you!

ERN-RND

European Academy of Neurology

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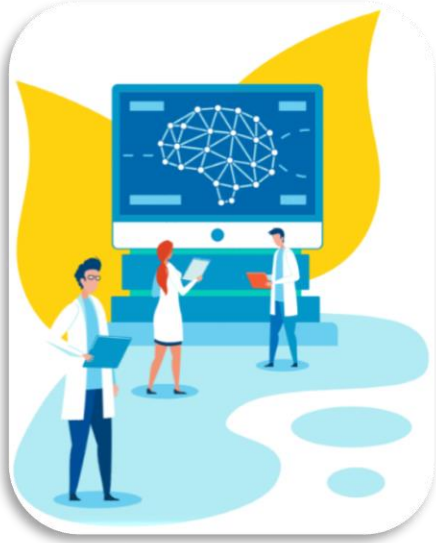
Joint webinar series



THANK YOU

Next Webinar:

‚Rehabilitation in ataxia: current evidence and practice‘
by Ludger Schöls

10. November 2020, 15-16h CET