UNIVERSITY OF BRESCIA

INTELLIGENZA ARTIFICIALE IN MEDICINA E INNOVAZIONE NELLA RICERCA CLINICA E METODOLOGICA

Coordinatore: Prof. Domenico Russo

# Cerebellar transcranial stimulation to treat neurodegenerative ataxia.

Dott.ssa Ilenia Libri

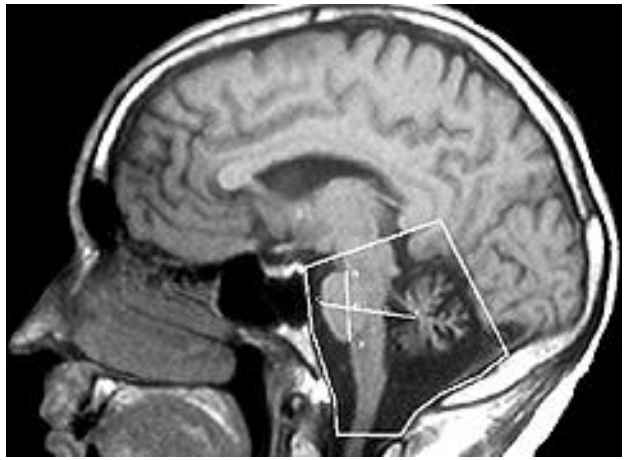
06 – 03 – 2025

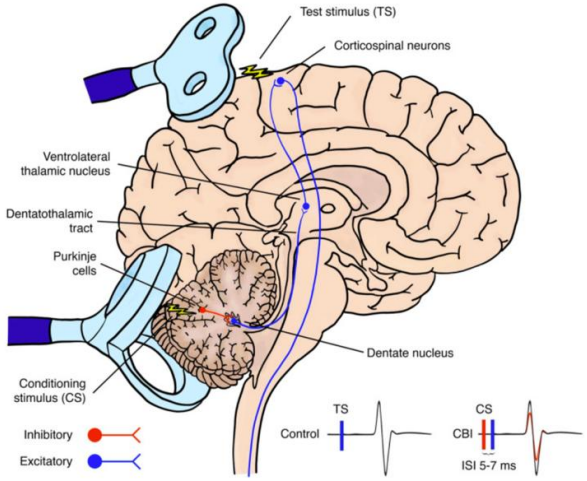
Supervisor: Prof.ssa Barbara Borroni

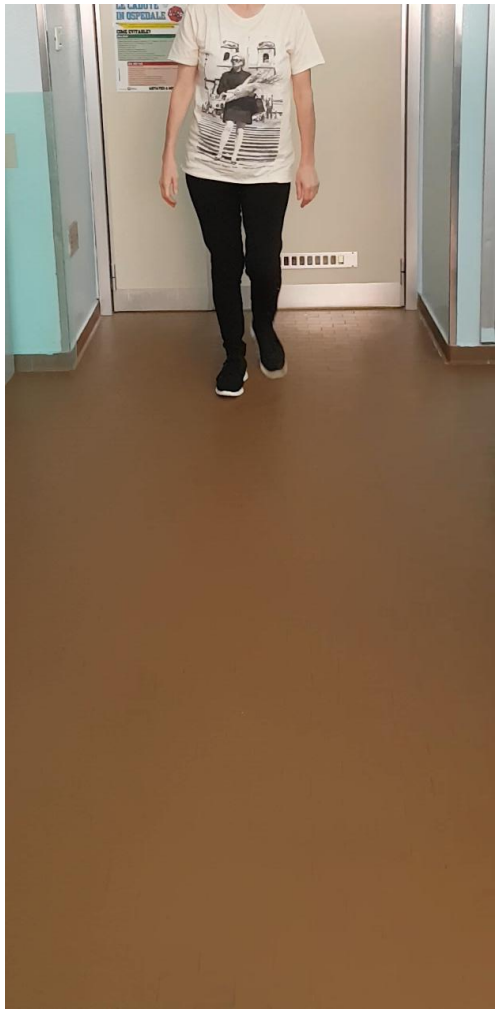
# Background

- Cerebellar ataxias are a very heterogenous group of degenerative disorders for which we currently lack effective and disease-modifying interventions.

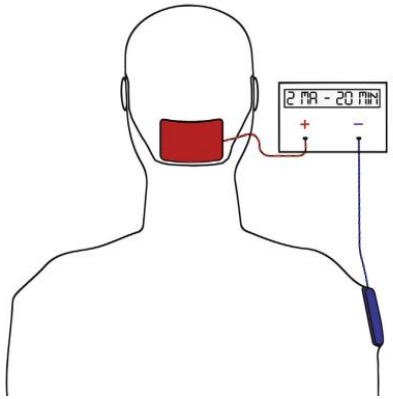
- Non-invasive cerebellar stimulation has been demonstrated to modulate cerebellar excitability and improve motor symptoms.





# Background



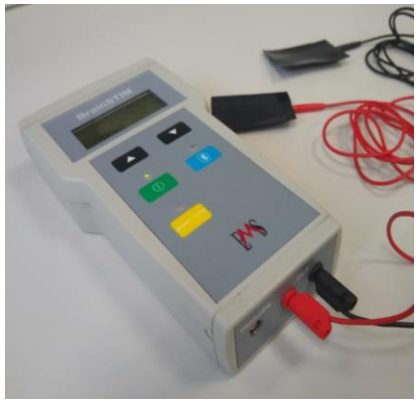


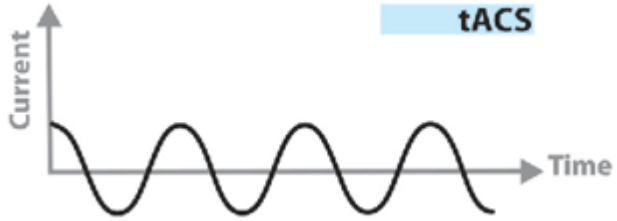
**Cerebellar tDCS**

Safe and non-invasive

Increased the excitability of the cerebellar cortex and thus CBI

Signifcant impact on motricity, cognition and quality of life






**Cerebellar tACS**

Safe and non-invasive

Gamma frequency band (30-80 Hz)

Modulation of cortical cerebellar oscillations has shown to induce cerebellar plasticity

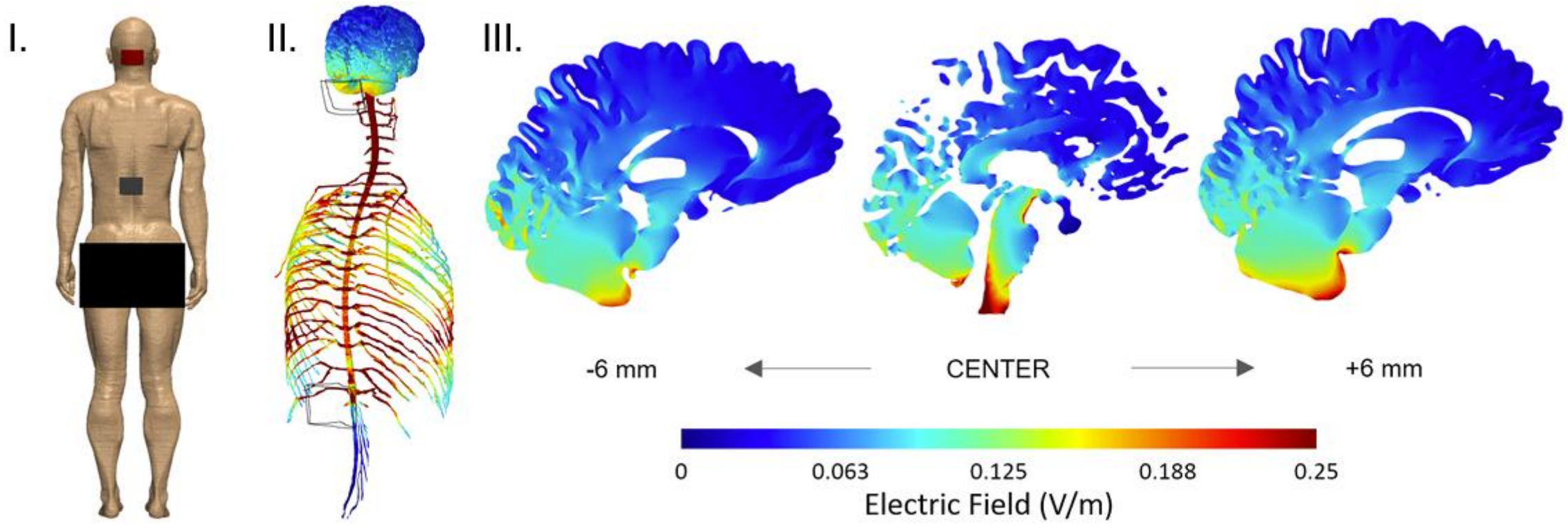
# Cerebellar tDCS

doi:10.1093/brain/awab157 BRAIN 2021: 144; 2310–2321

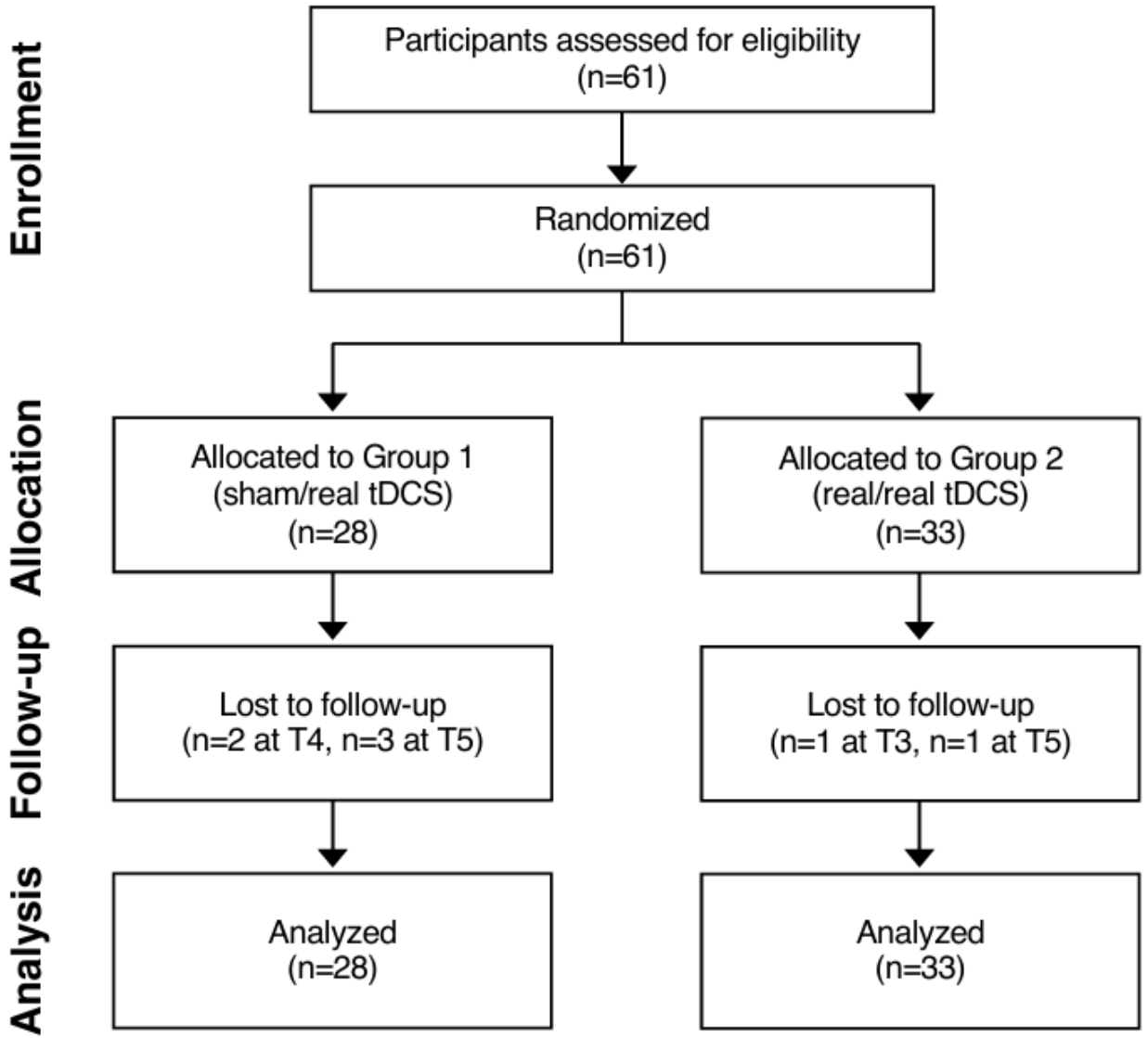
BRAIN
CLINICAL TRIAL

## Motor and cognitive outcomes of cerebello-spinal stimulation in neurodegenerative ataxia

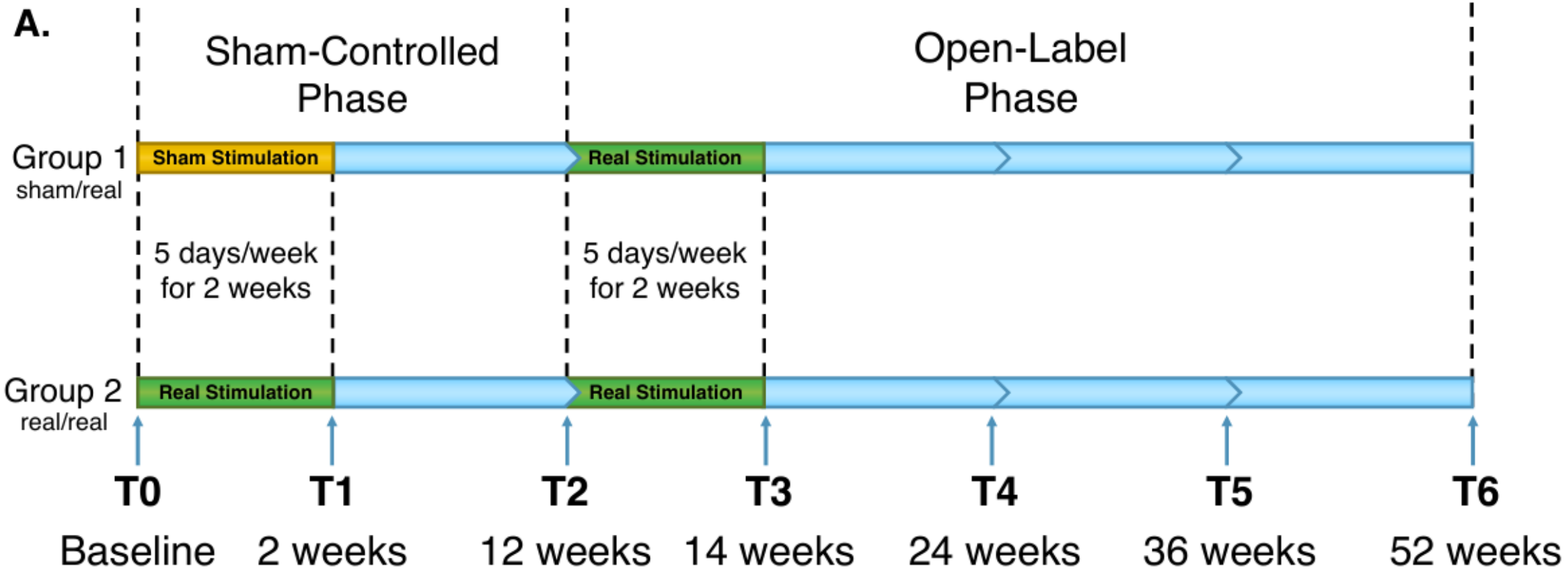
Alberto Benussi,[1,2] Valentina Cantoni,[1] Marta Manes,[1,3] Ilenia Libri,[1] Valentina Dell'Era,[1,4] Abhishek Datta,[5] Chris Thomas,[5] Camilla Ferrari,[6] Alessio Di Fonzo,[7,8] Roberto Fancellu,[9] Mario Grassi,[10] Alfredo Brusco,[11,12] Antonella Alberici[2,†] and Barbara Borroni[1,2,†]



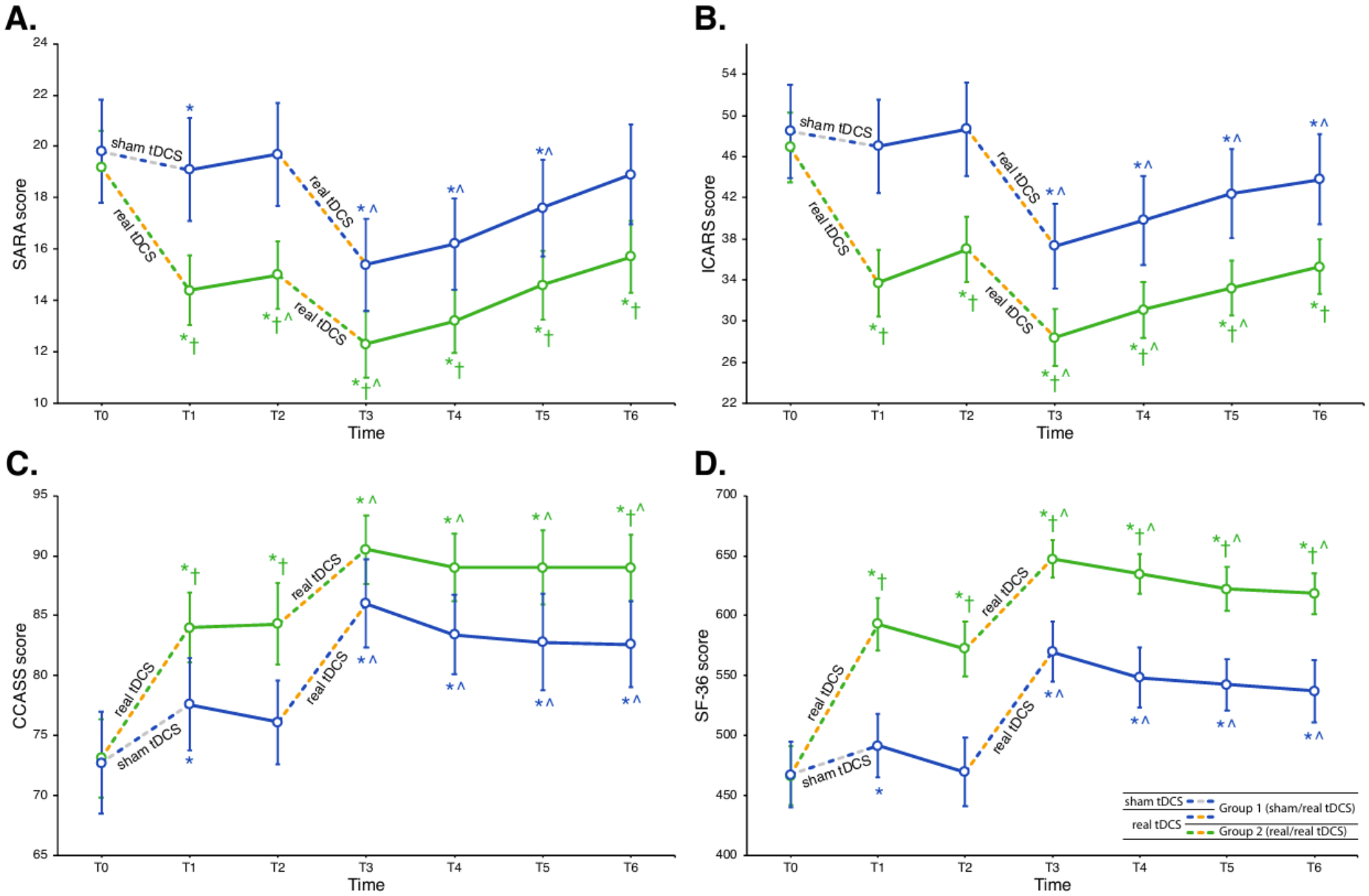
# tDCS - Flowchart



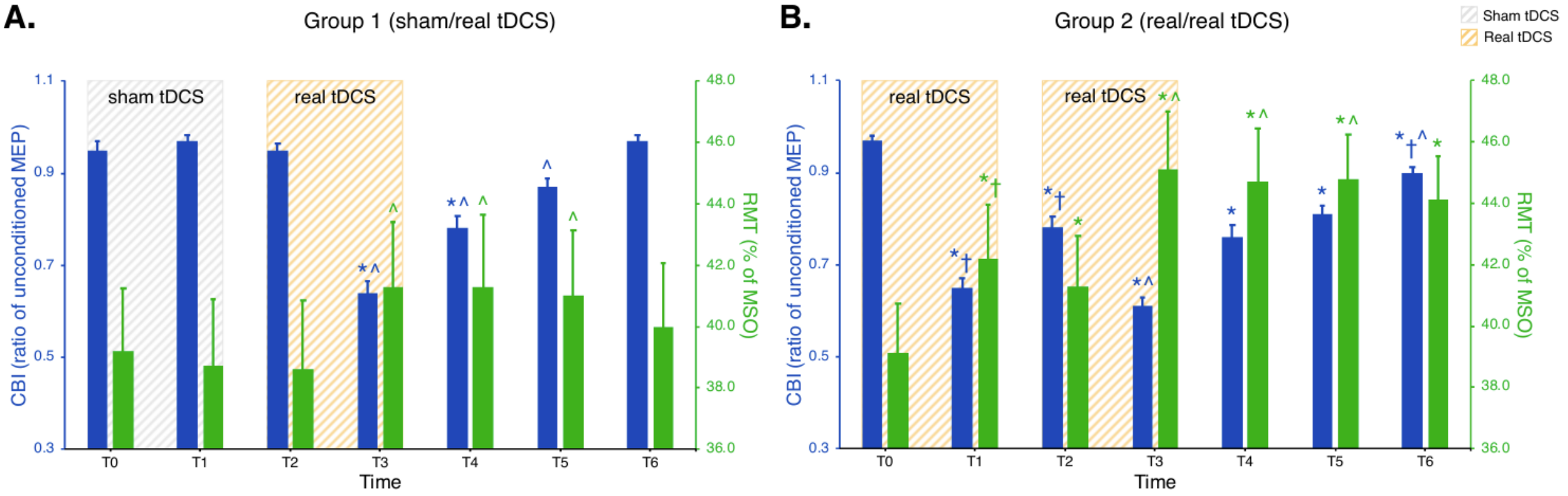
# tDCS – Study Design



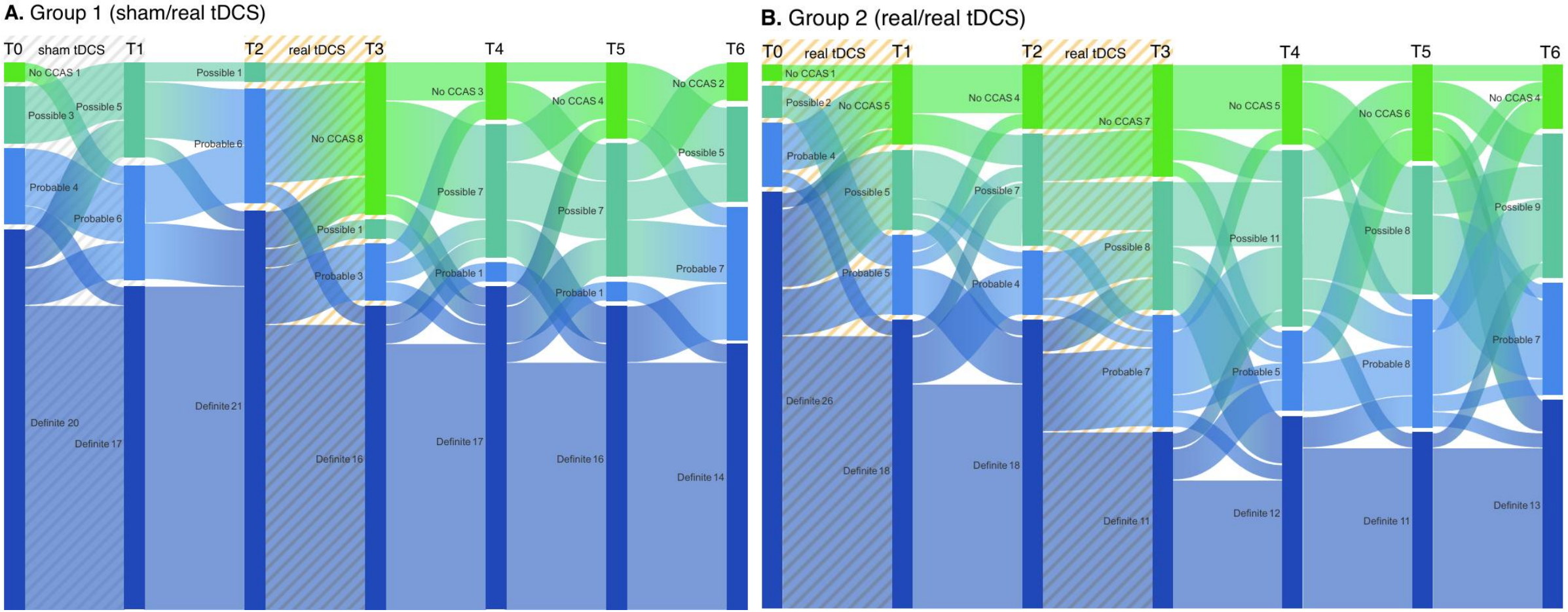
# tDCS - Results



# tDCS - Results



# tDCS - Results



# tDCS vs tACS

The Cerebellum (2024) 23:570–578
https://doi.org/10.1007/s12311-023-01578-6

RESEARCH

## Comparing Cerebellar tDCS and Cerebellar tACS in Neurodegenerative Ataxias Using Wearable Sensors: A Randomized, Double-Blind, Sham-Controlled, Triple-Crossover Trial

Ilenia Libri[1] · Valentina Cantoni[1] · Alberto Benussi[1,2] · Jasmine Rivolta[2] · Camilla Ferrari[3] · Roberto Fancellu[4] · Matthis Synofzik[5,6] · Antonella Alberici[2] · Alessandro Padovani[1,2] · Barbara Borroni[1,2]

# Objectives

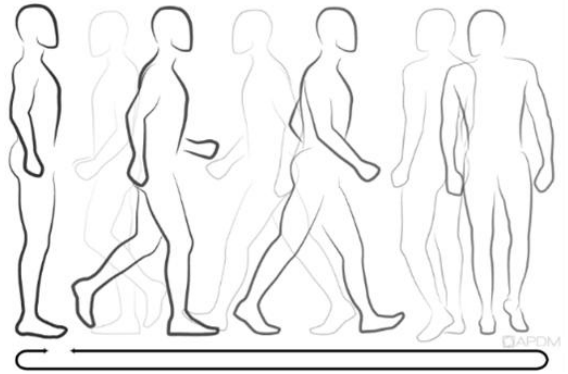
In this randomized, double-blind, sham-controlled, triple-crossover trial, we aimed at assessing which technique is superior in improving motor outcome in neurodegenerative ataxias.

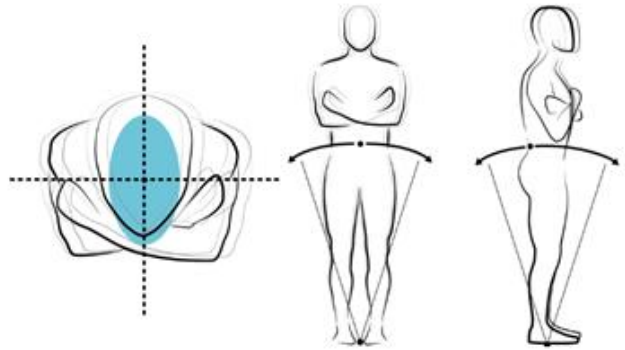
**Primary endpoints**

- Assessment and Rating of Ataxia (SARA)

**Secondary endpoint**

- State-of-the-art wearable sensors
- International Cooperative Ataxia Rating Scale (ICARS)
- Cerebello-cerebral connectivity (CBI)





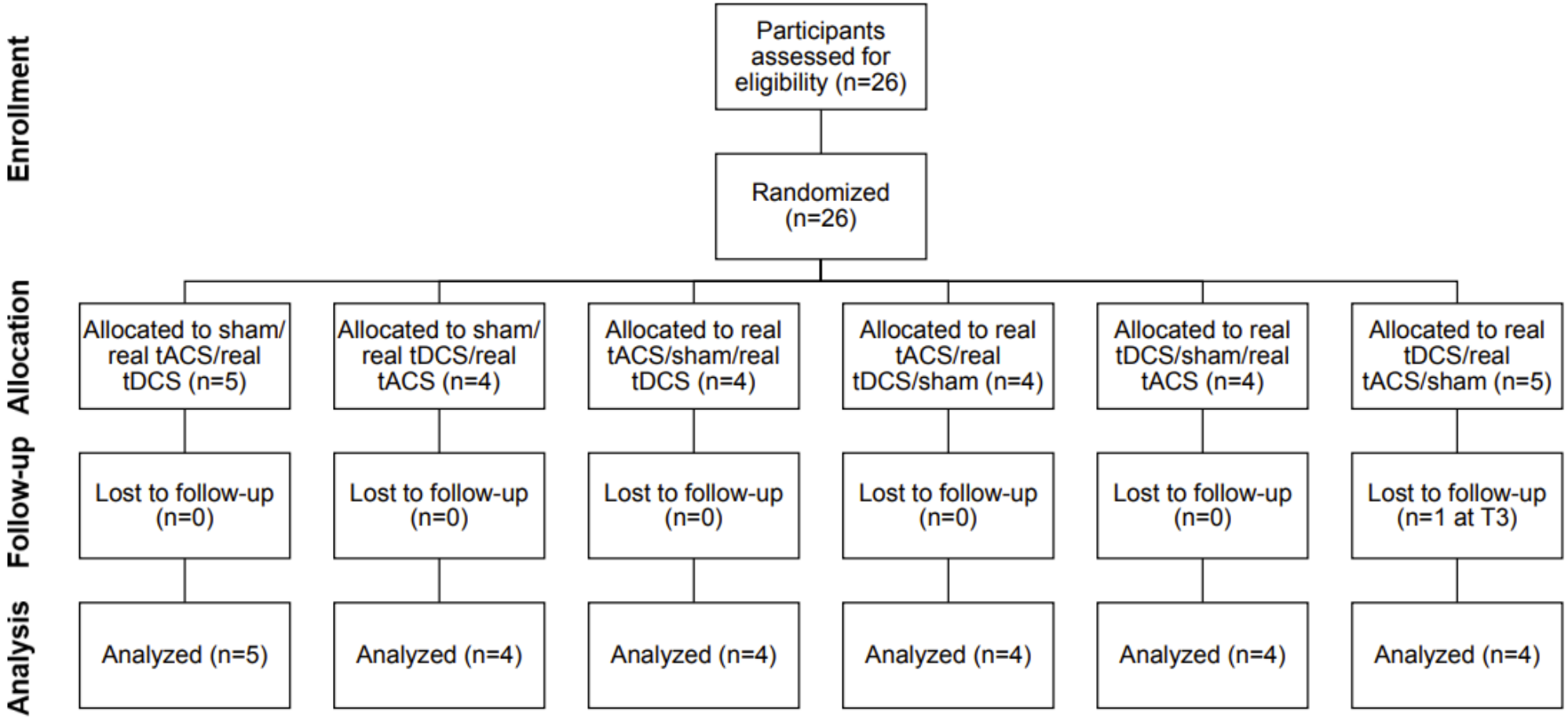
# Methods

## Demographic characteristics

| Patient | Age, y | Age at onset, y | Disease duration, y | Sex | Diagnosis | SARA | ICARS |
|---|---|---|---|---|---|---|---|
| 1 | 42 | 35 | 7 | M | SCA1 | 6 | 15 |
| 2 | 50 | 40 | 10 | F | SCA1 | 3 | 7 |
| 3 | 28 | 7 | 21 | F | AOA2 | 21 | 52 |
| 4 | 44 | 36 | 8 | M | SCA1 | 11.5 | 29 |
| 5 | 49 | 43 | 6 | F | SAOA | 9 | 23 |
| 6 | 34 | 32 | 2 | F | SAOA | 5 | 9 |
| 7 | 42 | 41 | 1 | M | SAOA | 4 | 13 |
| 8 | 51 | 47 | 4 | F | SAOA | 8 | 18 |
| 9 | 44 | 39 | 5 | F | SCA2 | 12 | 28 |
| 10 | 55 | 49 | 6 | F | SAOA | 3 | 11 |
| 11 | 23 | 20 | 3 | F | SCA2 | 14 | 38 |
| 12 | 70 | 68 | 2 | M | MSA-C | 12 | 23 |
| 13 | 59 | 57 | 2 | F | SAOA | 13.5 | 26 |
| 14 | 68 | 45 | 23 | F | SCA38 | 16 | 38 |
| 15 | 56 | 54 | 2 | F | SCA2 | 4 | 13 |
| 16 | 73 | 61 | 12 | F | MSA-C | 10 | 21 |
| 17 | 59 | 50 | 9 | M | SCA2 | 7 | 16 |
| 18 | 59 | 57 | 2 | M | SAOA | 12 | 27 |
| 19 | 48 | 45 | 3 | M | SAOA | 13 | 38 |
| 20 | 42 | 35 | 7 | M | SCA1 | 8 | 19 |
| 21 | 58 | 46 | 12 | M | SCA2 | 12 | 28 |
| 22 | 80 | 71 | 9 | M | SAOA | 5 | 12 |
| 23 | 68 | 64 | 4 | F | SAOA | 4.5 | 8 |
| 24 | 65 | 61 | 4 | F | SAOA | 3 | 6 |
| 25 | 39 | 34 | 5 | M | SCA1 | 9 | 17 |
| 26 | 59 | 50 | 9 | F | SAOA | 10 | 21 |

# Methods

## Study design



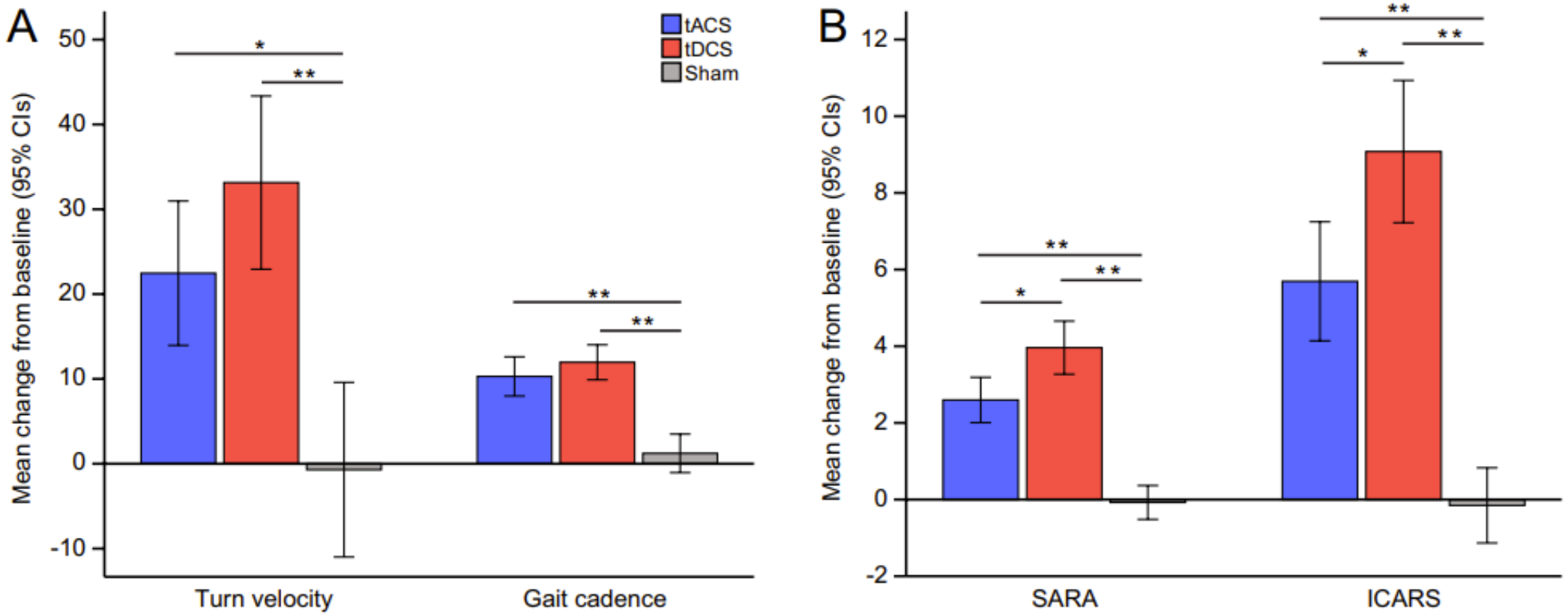
# Results

## Changes of wearable sensors scores and clinical scales after stimulations

| Variable | Baseline score (95%CI) | ΔtACS (95%CI) | ΔtDCS (95%CI) | Δsham (95%CI) | *p** |
|---|---|---|---|---|---|
| *Clinical scales* | | | | | |
| SARA | 9.1 (7.2–10.9) | 2.6 (2.0–3.2) | 4.0 (3.3–4.6) | −0.1 (−0.5–0.3) | <0.001 |
| ICARS | 21.4 (16.8–25.9) | 5.5 (4.1–7.2) | 9.1 (7.2–10.9) | −0.1 (−1.1–0.8) | <0.001 |
| *Wearable sensors* | | | | | |
| LL cadence, steps/min | 109.5 (103.3–115.7) | 10.3 (8.0–12.6) | 12.0 (9.9–14.0) | 1.2 (−1.1–3.5) | <0.001 |
| Turns velocity, degrees/sec | 148.8 (126.6–170.9) | 22.5 (13.9–31.0) | 33.1 (22.9–43.3) | −0.7 (−10.1–9.6) | <0.001 |
| Turns duration, sec | 4.3 (3.7–4.9) | 0.5 (0.1–1.0) | 1.1 (0.6–1.7) | 0.2 (−0.4–0.7) | 0.03 |

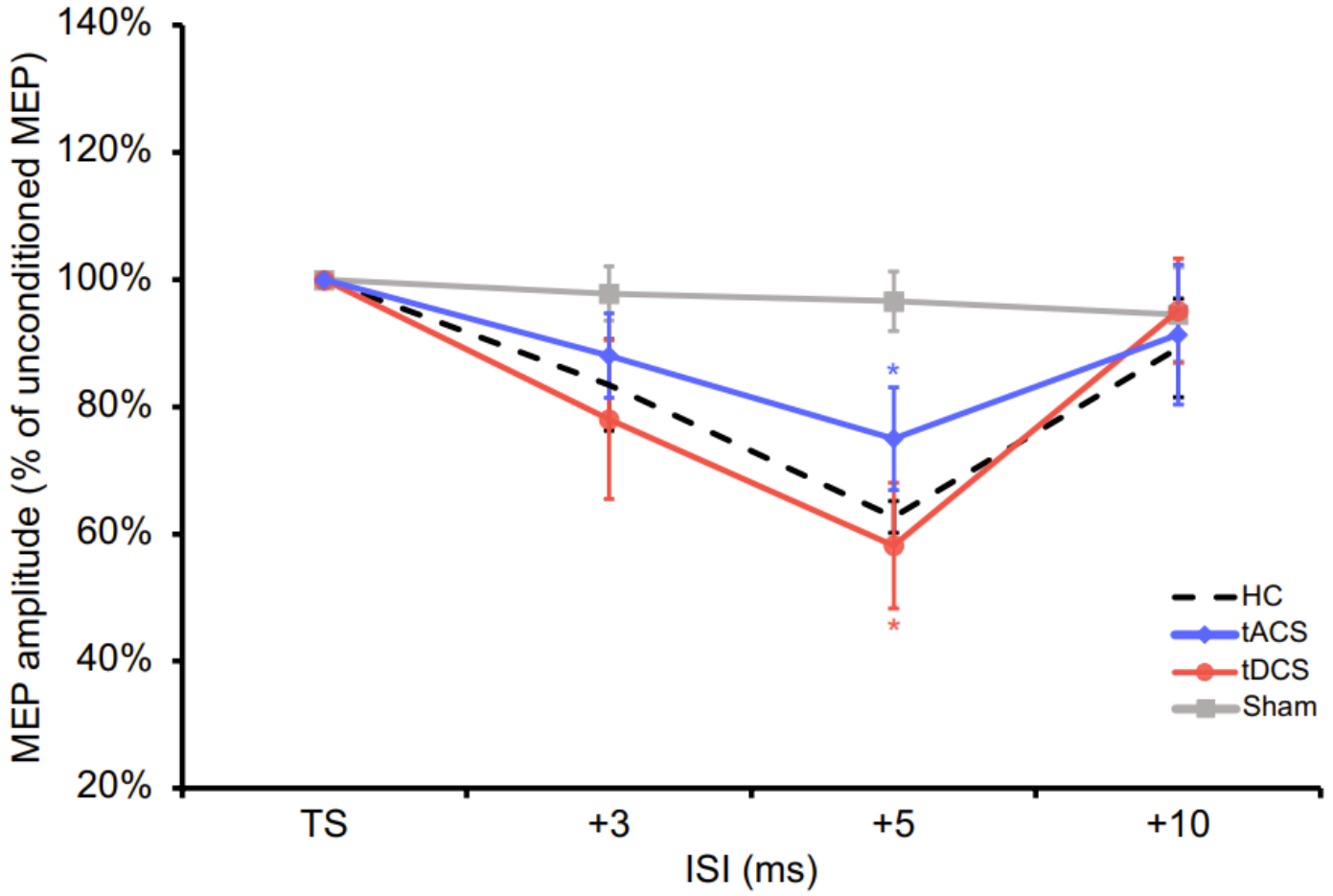
# Results

**Changes in A wearable sensors parameters and B clinical scores compared to baseline**



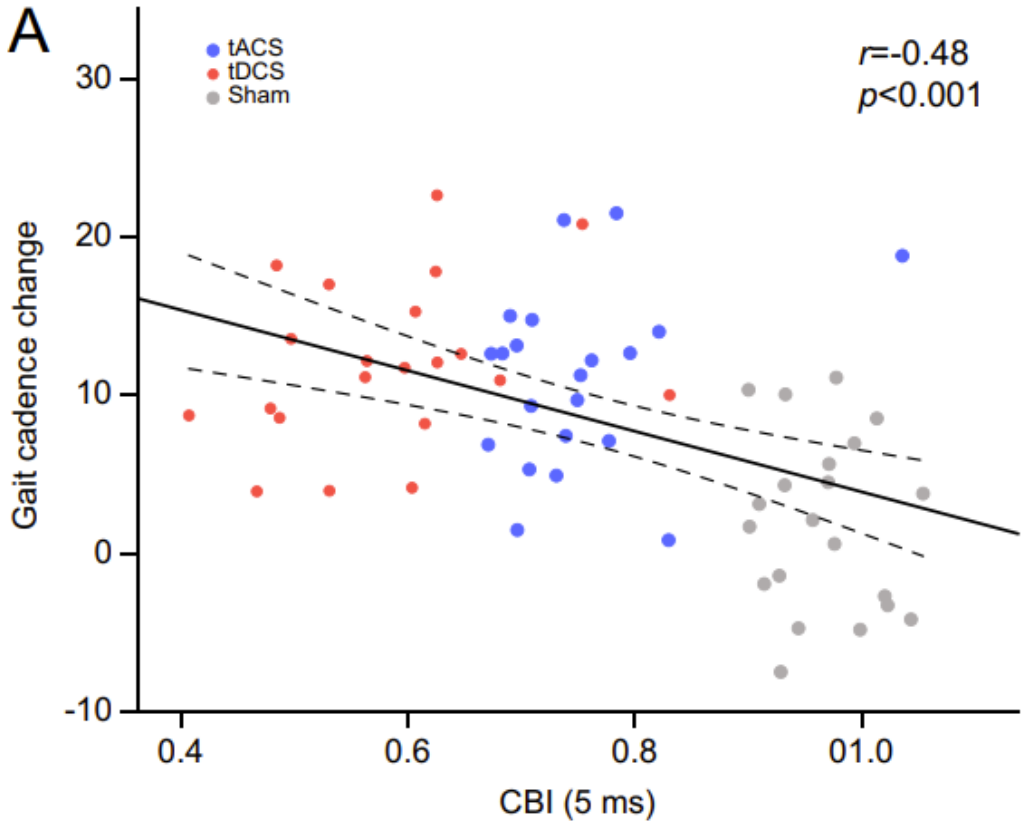
# Results

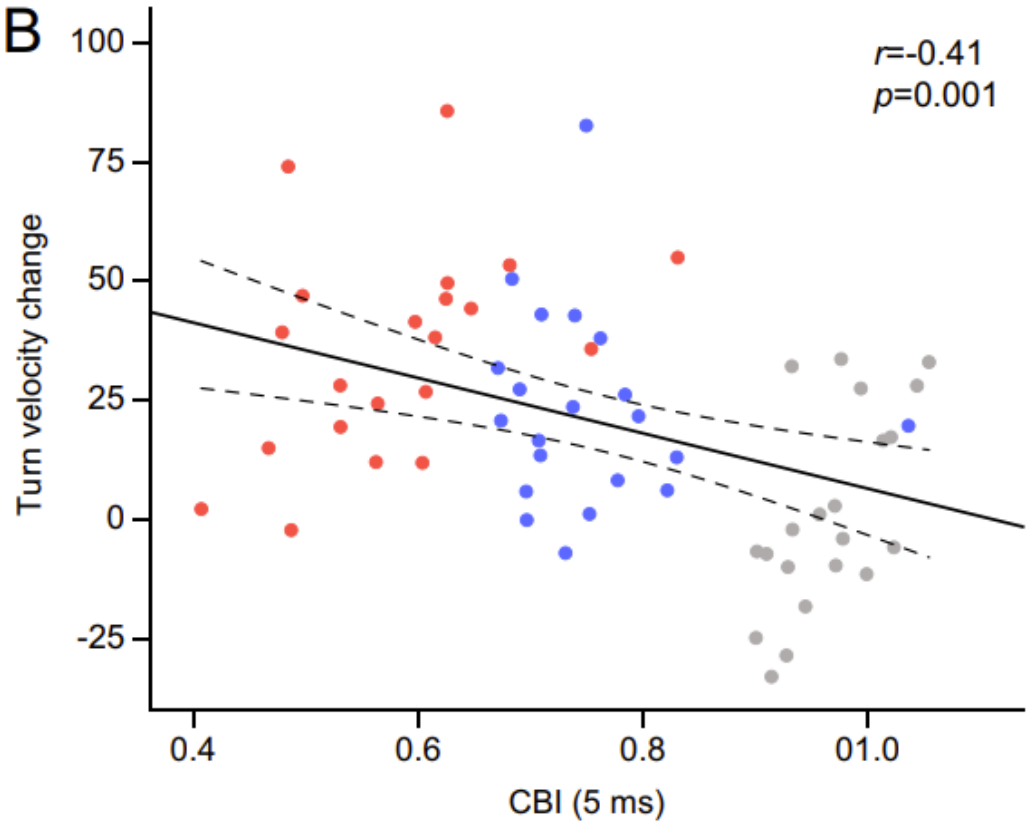
## Cerebellar inhibition (CBI)

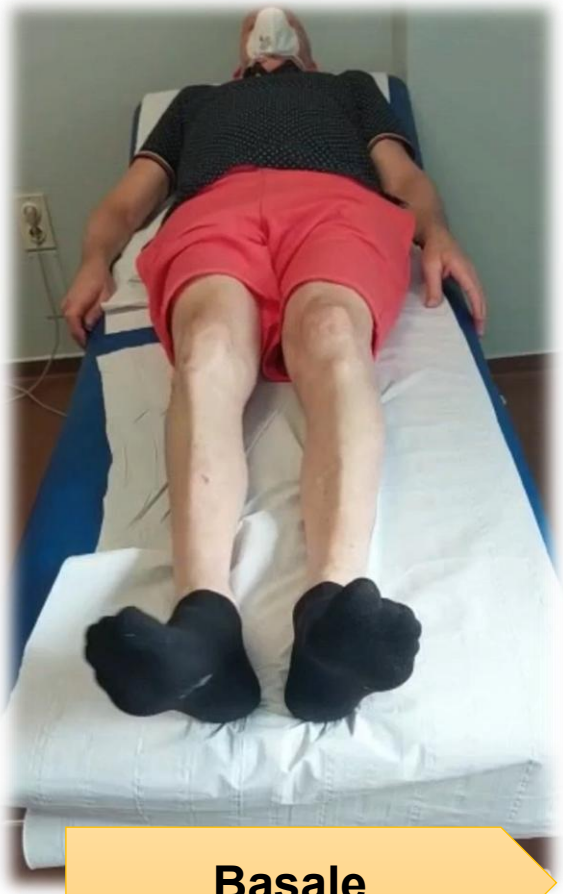


# Results

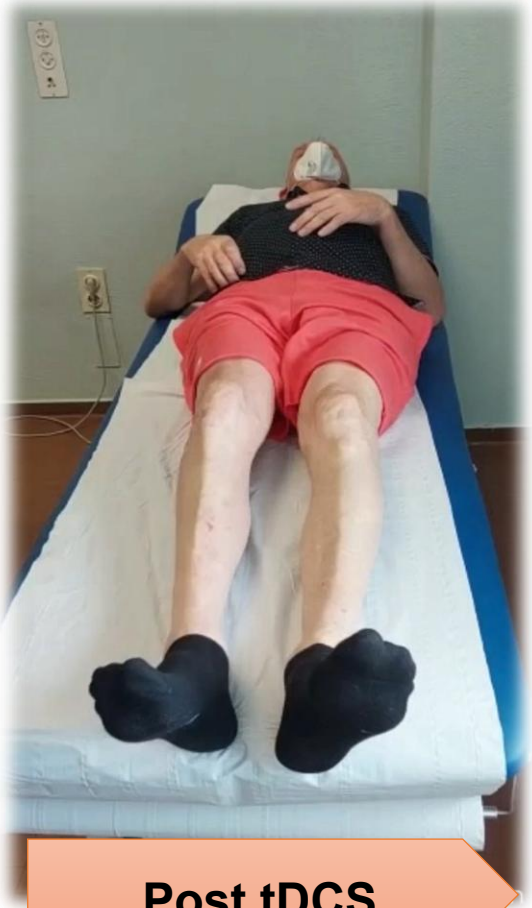
**Correlation analyses between sensor-based measures and CBI scores after intervention**



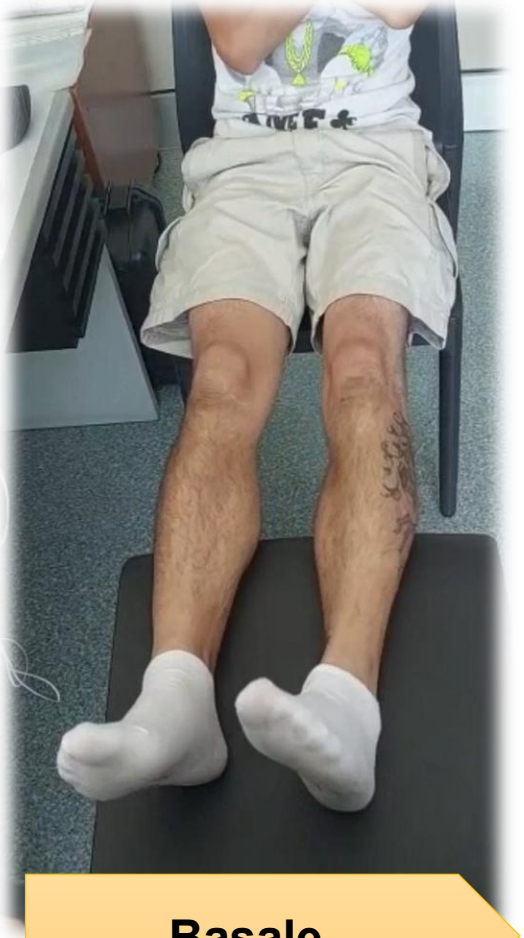





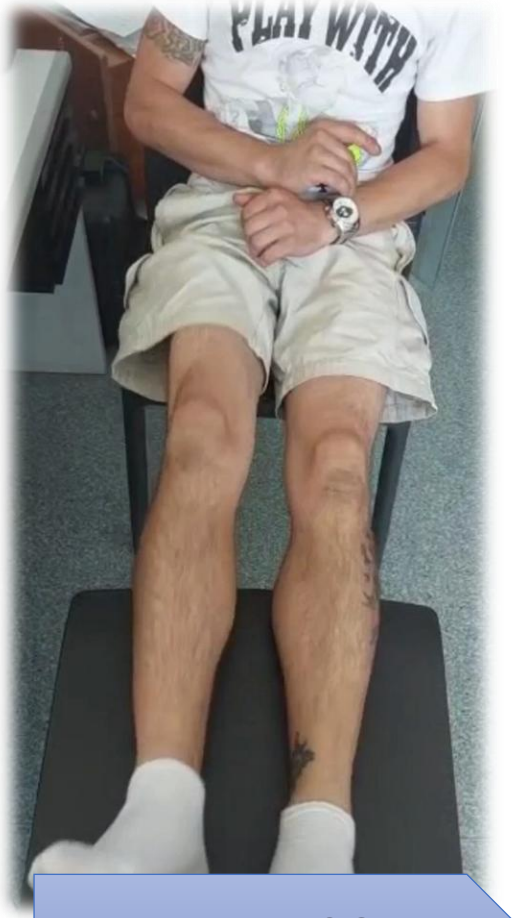
Basale



Post tDCS



Basale




Post tACS

# Conclusions

Significant *improvement of motor symptoms* with both approaches.

*Cerebellar tDCS* as the best therapeutic intervention candidate in neurodegenerative ataxias.

*Restoration of neurophysiological measures* of motor cortex excitability and cerebellar-cerebral connectivity.

*Digital motor biomarkers* as outcome measures for future treatments trials.

# Limitations and future perspectives

Heterogenous groups

Relatively small sample

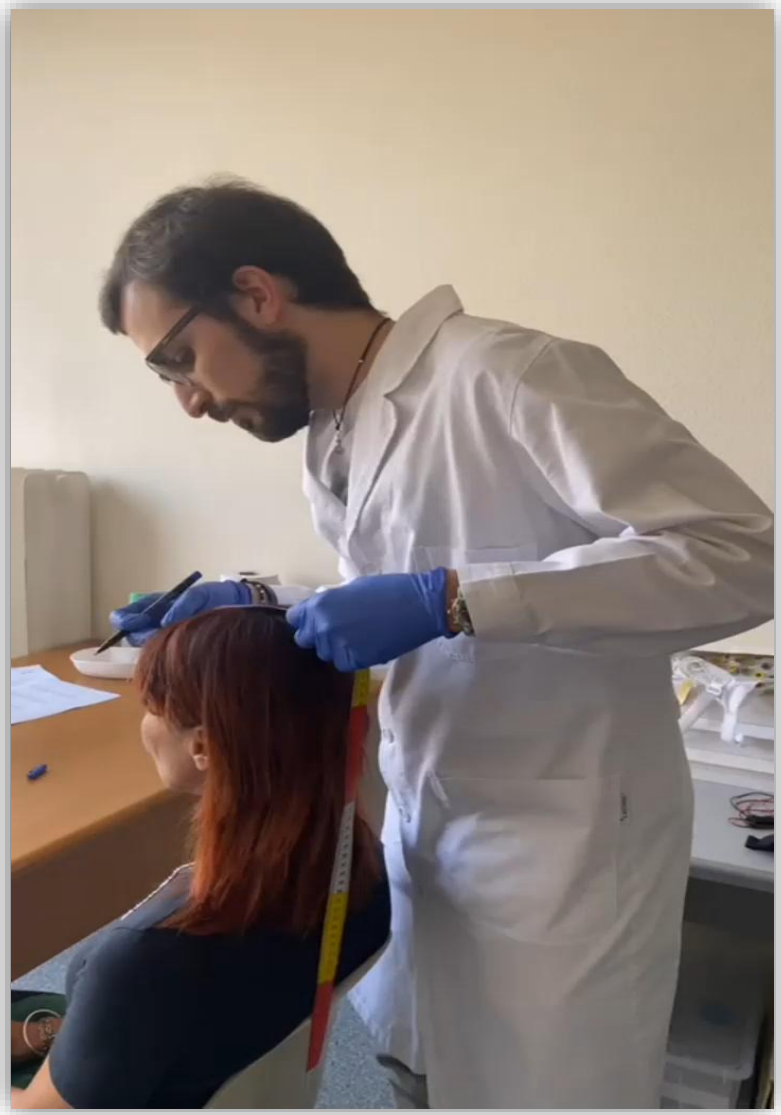
Multicenter studies

Long-term effects

**tDCS**

**efficacy in at-home settings?**

# tDCS at home



- **helmet customization** for each patient
- first 3-5 sessions in hospital under supervision of dedicated staff and **training of the caregivers** on the use of the device
- **videocalls** during first home sessions and **daily telephone contact** availability with dedicated staff
- **remote verification** of the number of sessions carried out via daily code

# tDCS at home - Objectives

Randomized, double-blind, sham-controlled trial.

**Primary endpoints**

To assess **safety, tolerability and clinical efficacy** of multisessions cerebellar tDCS in at-home setting.

- State-of-the-art wearable sensors
- Assessment and Rating of Ataxia (SARA)
- International Cooperative Ataxia Rating Scale (ICARS)
- CCASS

# tDCS at home - Objectives

## Secondary endpoints

To assess the **biological effects** of multiple sessions of anodal cerebellar tDCS.

- Neurofilament light (NfL) and glial fibrillary acidic protein (GFAP)
- FDG-PET

## Tertiary endpoints

Dissemination and impact.

# tDCS at home - Method




Patients were randomized in **two groups** for the first controlled phase.

At baseline (T0), Group 1 received placebo stimulation (**sham tDCS**) while Group 2 received **real tDCS** for 5 days/week for 4 weeks (T1), with 12-week (T2) follow-up (randomized, double-blind, sham controlled phase).

At the 12-week follow-up (T2), all patients (Group 1 and Group 2) received a second treatment of real tDCS for 5 days/week for 4 weeks, with a 16-week (T3), 28-week (T4), 40-week (T5) (open-label phase).

# tDCS at home – Statistical Analyses

To assess the effect of tDCS treatment on clinical scores and neurophysiological measures over time, we used a two-way mixed analysis of covariance (**ANCOVA**) with TIME as within-subject factors and TREATMENT (real/real stimulation vs sham/real stimulation) as between-subject factors.

Baseline values of each score were used as covariates, to reduce possible effects of baseline characteristics on clinical score changes over time.

Moreover, we separately evaluated effects of TIME and TREATMENT in the randomized, double-blind phase and in the open-label phase.

# tDCS at home – Results

**In progress..**

# Acknowledgment


- **Neurology Unit, Departement of Clinical and Experimental Sciences, University of Brescia, Italy**
  Prof. Alessandro Padovani
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