UNIVERSITY OF TRIESTE

MDS-ES Diagnosis and Treatment of Cerebellar Ataxias

Non-Pharmacological Treatment in Ataxia

Alberto Benussi, MD

CONFLICTS OF INTEREST

Disclosures

- Alberto Benussi has received financial support from Fondazione Airalzh, the Cariplo Foundation, the Ministero dell'Università e della Ricerca, and the Fondation Recherche Alzheimer.
- He has received honoraria for lectures and presentations from Angelini Pharma, Eisai, Eli Lilly, Novo Nordisk, and Sun Yat-Yat-sen University.
- He has received consulting fees from AlphaSights, Eisai, Roche, Simon-Kucher & Partners, Health Advances, and the European Commission.
- He has received advisory board fees from Eisai and Eli Lilly.
- He is listed as an inventor on patents on the use of non-invasive brain stimulation for the differential diagnosis of dementia and to increase cognitive functions in patients with neurodegenerative disorders.

Outline

I **The clinical problem**

Why hundreds of diseases can share one treatment strategy

II **Physical rehabilitation**

Coordinative training, intensity and durability

III **Allied & supportive therapies**

Occupational therapy, speech, swallowing, the team

IV **Non-invasive brain stimulation**

Mechanisms, montages, dosing and the trial evidence

V **Horizon & synthesis**

Invasive neuromodulation, the future, an integrated pathway

AUDIENCE POLL

Which non-pharmacological approach do you think has the strongest randomised evidence in ataxia today?

A Intensive coordinative physiotherapy

C Cerebellar rTMS

B Cerebellar tDCS

D None has RCT-level evidence yet

AUDIENCE POLL

Which non-invasive brain stimulation approach has the strongest randomised evidence in ataxia?

A Cerebellar rTMS

C Cerebellar tACS

B Cerebellar tDCS

D Cerebellar tRNS

PART I

The clinical problem

Why a single, cause-independent treatment strategy is not a compromise — it is a necessity.

THE CLINICAL PROBLEM

The ataxias: a large and heterogeneous family

Cerebellar ataxia is a single clinical syndrome produced by **hundreds of distinct diseases**. They differ in gene, mechanism, age of onset and progression, but converge on the same motor phenotype.

Hereditary

Autosomal dominant — >40 SCA subtypes; Autosomal recessive — Friedreich ataxia, AT, ARSACS; X-linked — FXTAS; Mitochondrial

Acquired

Immune — gluten, anti-GAD, paraneoplastic; Toxic / metabolic — alcohol, drugs, vitamin E; Vascular & structural; Infectious / post-infectious

Sporadic degenerative

Multiple system atrophy, cerebellar type (MSA-C); Sporadic adult-onset ataxia (SAOA); Genetically unexplained late-onset

Klockgether, Mariotti & Paulson (2019), *Nat Rev Dis Primers* 5:24.

THE CLINICAL PROBLEM

Epidemiology and the diagnostic gap

Each subtype is rare, but collectively the ataxias are among the more common causes of chronic progressive incoordination.

≈2.7

per 100,000 — autosomal **dominant** hereditary ataxia

≈3.3

per 100,000 — autosomal **recessive** hereditary ataxia

≈1 in 3

progressive ataxias remain **genetically unexplained** after work-up

The consequence: for the great majority of patients — regardless of subtype — no therapy modifies the disease. Management is, of necessity, symptomatic and functional.

Ruano et al. (2014), *Neuroepidemiology* 42:174. · de Silva et al. (2019), *Orphanet J Rare Dis* 14:51.

THE CLINICAL PROBLEM

The therapeutic bottleneck

Disease-modifying strategies are, by design, **cause-specific** — one molecular target per genotype. Against hundreds of causes, this cannot serve most patients.

Hundreds of distinct causes

Alcohol / toxic · Gluten ataxia · Anti-GAD · Paraneoplastic · Multiple sclerosis · Vascular · MSA-C · Friedreich ataxia · SCA3 · SCA2 · SCA1 · SCA6 · SCA7 · Vitamin E / B12 deficiency · SAOA · FXTAS · Ataxia-telangiectasia · ARSACS · SCA8 · SCA17 · DRPLA · Episodic ataxia · POLG-related · Superficial siderosis · Post-infectious · SCA10 · SCA14

+ hundreds more

one target at a time

A few in clinical trials

Antisense & gene-targeted programmes for select genotypes (e.g. SCA1/2/3, FRDA)

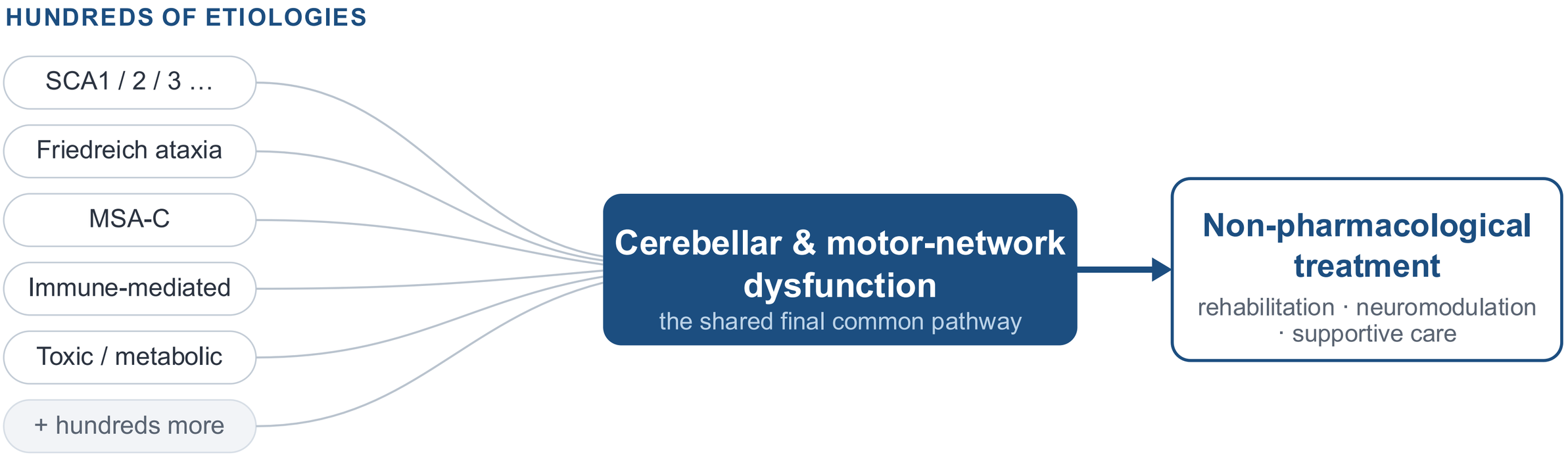
The majority — nothing targeted

No disease-modifying option exists for most of the family, and none is imminent.

Klockgether, Mariotti & Paulson (2019), *Nat Rev Dis Primers* 5:24.

THE CLINICAL PROBLEM · THE CENTRAL IDEA

Convergence on a shared final common pathway



> Because these interventions act **downstream of the cause**, a single strategy can serve the whole family — whatever the genotype, and even when the diagnosis is unknown.

Rationale after Ilg et al. (2014), *Cerebellum* 13:248; Benussi, Pascual-Leone & Borroni (2020), *Int J Mol Sci* 21:1948.

ASSESSMENT

Measuring ataxia: outcome measures for clinical trials

Instrument	Structure	Range	Notes
SARA Scale for the Assessment and Rating of Ataxia	8 items — gait, stance, sitting, speech, finger-chase, nose–finger, fast alternating movements, heel–shin	**0 – 40**	Quick (~15 min); the dominant clinical & trial endpoint
ICARS International Cooperative Ataxia Rating Scale	19 items across 4 subscales — posture/gait, kinetic, speech, oculomotor	**0 – 100**	Older, more detailed; longer to admixnister
Timed function objective performance	8-metre walk time (8MWT); 9-hole peg test (9HPT)	**seconds**	Sensitive to change; gait speed & dexterity
Patient-reported activity & participation	PROM-Ataxia; health-related quality-of-life measures	**varies**	Capture what matters to patients

Schmitz-Hübsch et al. (2006), *Neurology* 66:1717 (SARA); Trouillas et al. (1997), *J Neurol Sci* 145:205 (ICARS).

PART II

Physical rehabilitation

The evidence-backed backbone — and the benchmark every other modality should be measured against.

PHYSICAL REHABILITATION

The rationale for rehabilitation in cerebellar degeneration

The rationale

Although the cerebellum is central to motor learning, useful learning capacity is **partly preserved** even in degeneration — and training additionally recruits **compensation** through cortical and spinal networks.

The goal is not repair but to **slow functional decline** and expand what the patient can do.

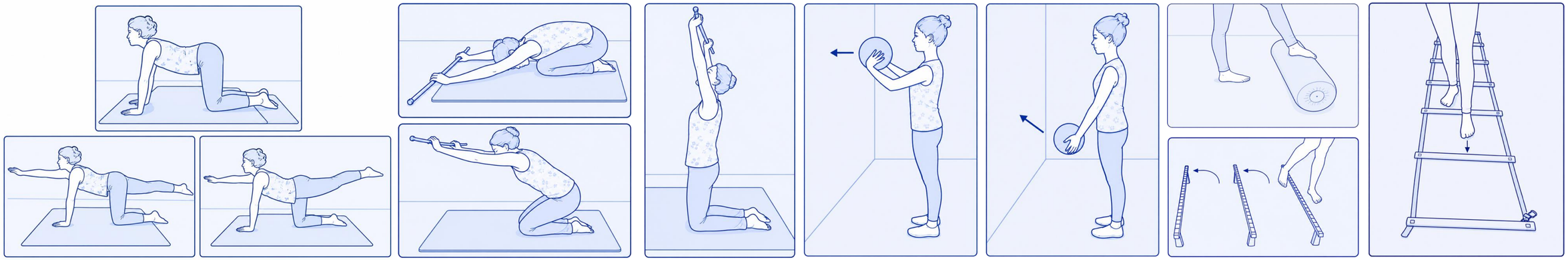
Principles of effective training

01 **Intensity & dose** — high volume, sustained over weeks

02 **Task-specific & coordinative** — whole-body balance and multi-joint control

03 **Repetition & feedback** — many trials, augmented feedback

04 **Continuity** — gains fade without ongoing practice



Ilg et al. (2014), *Cerebellum* 13:248; Synofzik & Ilg (2014), *Biomed Res Int* 583507; Chien et al. (2022), *Arq Neuropsiquiatr* 80:306

PHYSICAL REHABILITATION · FOUNDATIONAL EVIDENCE

Coordinative training: the first controlled evidence

DESIGN

16 patients — cerebellar (n=10) or afferent (n=6) ataxia · 4-week intensive coordinative training · intra-individual control design

ALSO IMPROVED

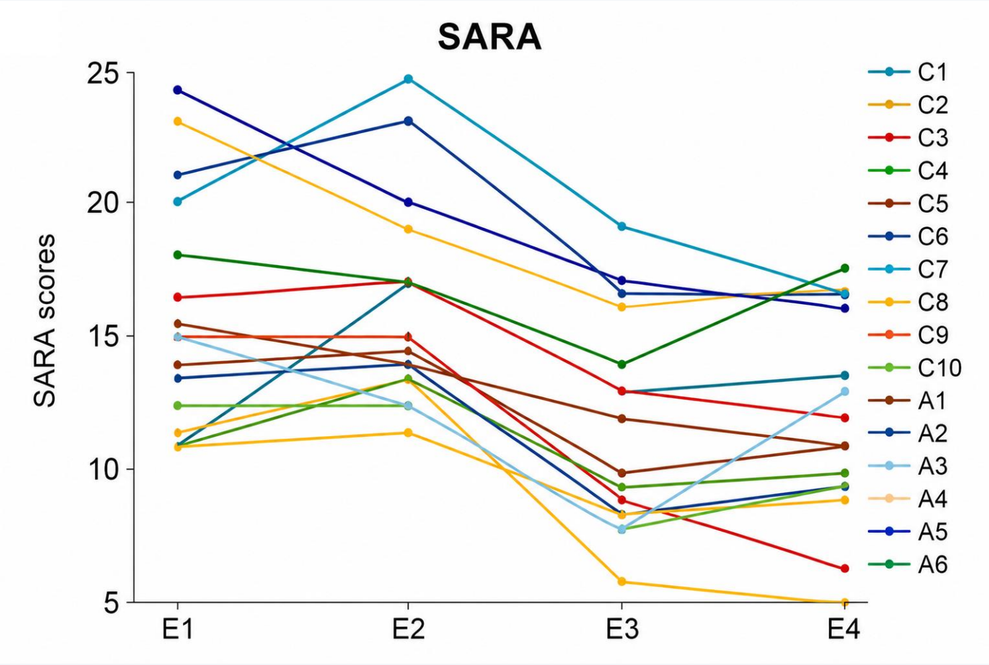
ICARS · quantitative gait & balance measures · individual goal-attainment

EVIDENCE

Class III — first controlled proof that a degenerating cerebellum remains trainable

SARA score

lower is better



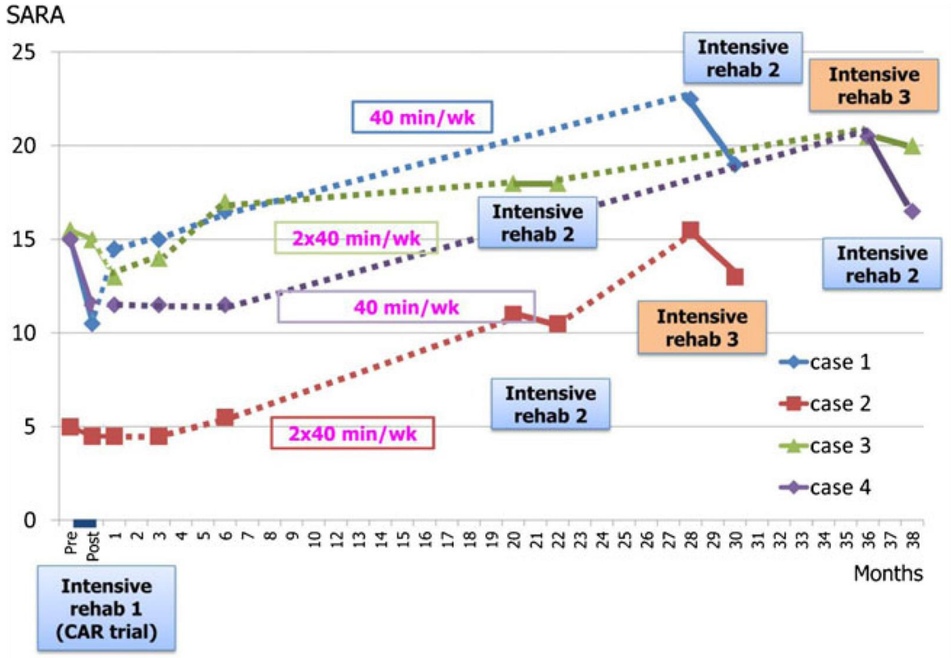
Ilg et al. (2009), *Neurology* 73:1823.

PHYSICAL REHABILITATION · DURABILITY

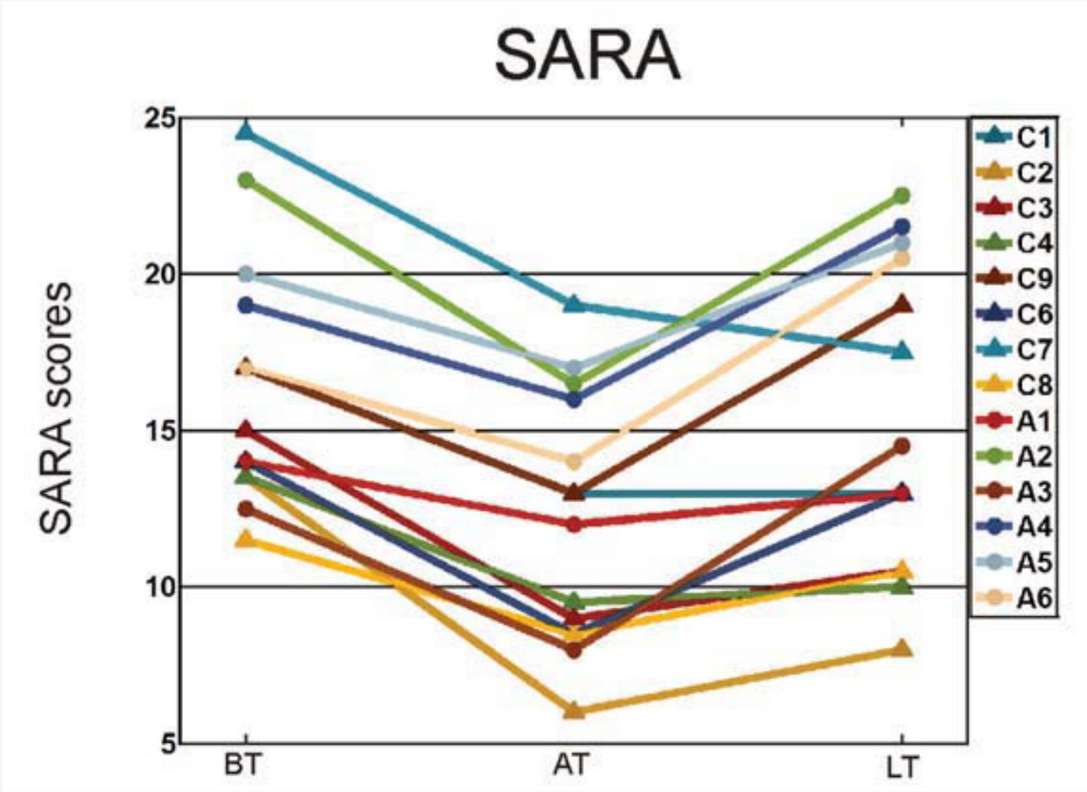
Durability of benefit and the need for continued training

At **one-year follow-up**, coordinative-training gains can persist — **conditional on continued practice**.

- **Continued home training** — improvement holds
- **Training stopped** — regression toward baseline



Motor performance over time



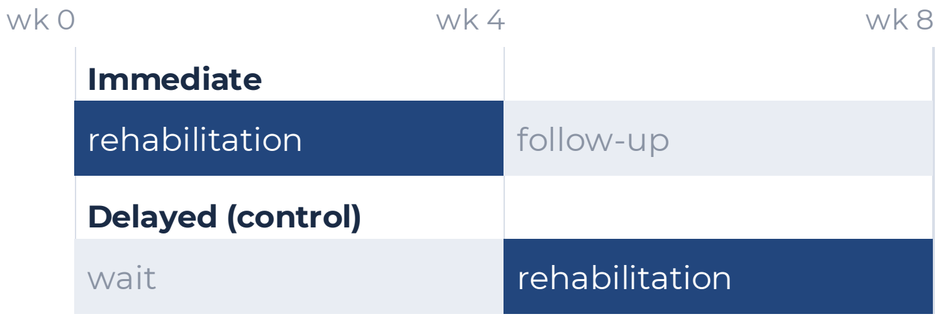
Ilg et al. (2010), *Mov Disord* 25:2239; Miyai et al. (2012), *Neurorehabil Neural Repair 26:515*.

PHYSICAL REHABILITATION · RANDOMIZED EVIDENCE

Intensive inpatient rehabilitation (CART trial)

DESIGN

42 patients, pure cerebellar degeneration · randomized immediate vs delayed-entry · 4 weeks inpatient PT + OT, ~2 h/day · coordination, balance, ADL



Outcomes

- ↓ **Ataxia severity (SARA)** — significant improvement
- ↑ **Gait speed** — faster, longer walks
- ↑ **Activities of daily living** — functional gains

Maintained at **12 weeks**; waning by 24 — continuity again decisive.

	Baseline	4 Weeks	Change	Between-group Δ (95% CI)	P
SARA total (max 40)					
Immediate	12.2 (0.7)	9.3 (0.8)	−2.8 (0.4)	−3.0 (−4.3 to −1.8)	<.001
Delayed	11.0 (0.8)	11.4 (0.8)	0.3 (0.4)		
FIM total (max 126)					
Immediate	118.5 (1.2)	119.8 (1.1)	1.2 (0.3)	1.3 (0.3 to 2.3)	<.05
Delayed	120.4 (1.2)	120.1 (1.1)	−0.2 (0.3)		
Gait speed (m/s)					
Immediate	0.813 (0.069)	0.954 (0.071)	0.137 (0.030)	0.110 (0.024 to 0.196)	<.01
Delayed	0.898 (0.069)	0.923 (0.071)	0.027 (0.030)		

Values: mean (SE). Between-group Δ favours the immediate group; baseline differences NS for all measures.

Miyai et al. (2012), *Neurorehabil Neural Repair* 26:515.

PHYSICAL REHABILITATION

Balance, gait and falls prevention

THE BURDEN

~3 in 4

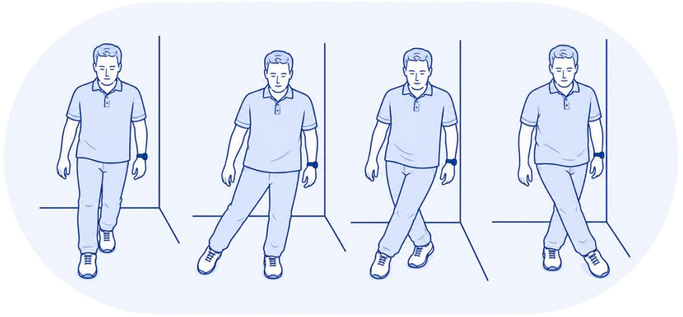
patients with cerebellar ataxia **fall within a year**; high rate of fall-related injuries (74%).

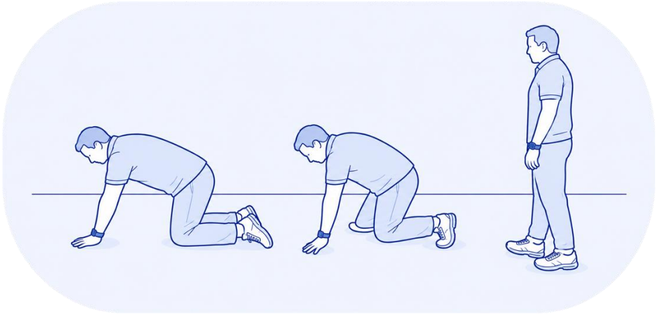
Factors that were associated with a higher fall frequency included: disease duration, severity of ataxia, the presence of pyramidal symptoms, the total number of non-ataxia symptoms, and the genotype SCA3

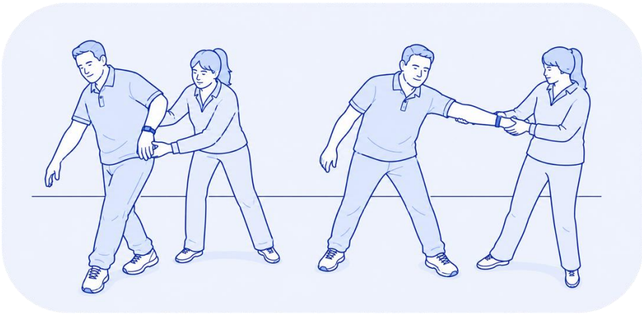
WHAT TRAINING TARGETS

- Static & dynamic balance
- Dual-task practice
- Reactive / perturbation balance
- Gait & treadmill training
- Whole-body coordination
- Falls-prevention strategy

Systematic review: balance/postural training **improves stability measures**, with falls reduction in several controlled studies.







Fonteyn et al. (2010), *Cerebellum* 9:232; Marquer et al. (2014), *Ann Phys Rehabil Med* 57:67; Chien et al. (2022), *Arq Neuropsiquiatr* 80:306

PHYSICAL REHABILITATION · TECHNOLOGY

Technology-assisted training: exergames & VR

Whole-body-controlled **exergames** produced measurable reductions in ataxia and improved coordination in children with degenerative ataxia — the effect sizes rivalling conventional intensive training.

Their advantage is behavioural: engagement sustains **high-dose, home-based practice** with rich real-time feedback. VR and robotic platforms extend the same principle.

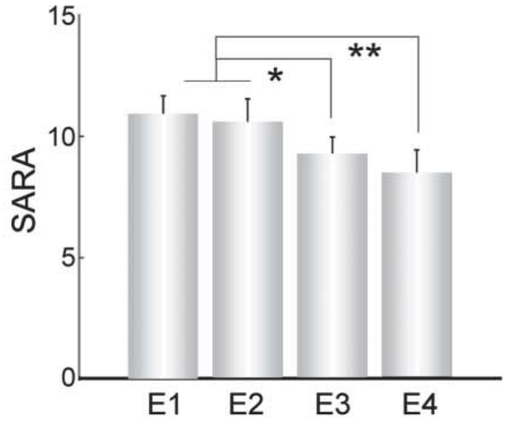
Engaging games

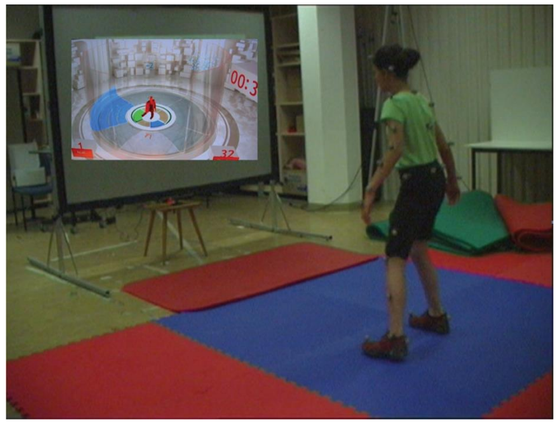
↓

Sustained high-dose practice

↓

Coordinative improvement





Ilg et al. (2012), *Neurology* 79:2056; Synofzik & Ilg (2014), *Biomed Res Int* 583507.

PHYSICAL REHABILITATION · ADJUNCTS

Treadmill, robotics, weighting and biofeedback

Treadmill training

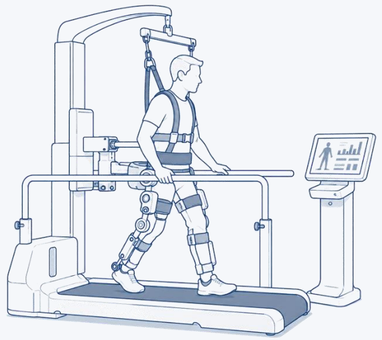
Low

± bodyweight support — improves gait speed and variability in small studies.

Robotic-assisted gait

Emerging

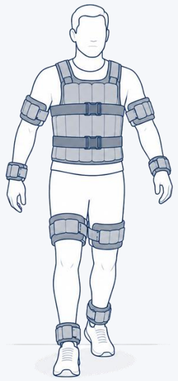
Feasible and reproducible dosing, but controlled data remain sparse.



Torso / limb weighting

Very low

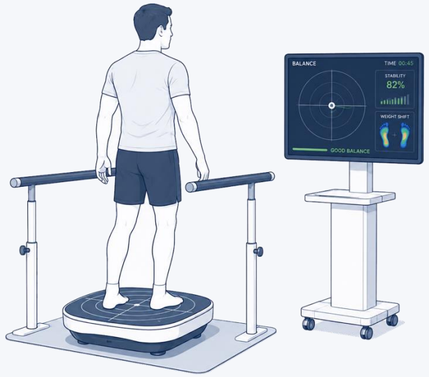
Aims to damp ataxic sway — but benefit is inconsistent and rarely durable.



Balance biofeedback

Low

Visual / vibrotactile cueing gives short-term gains in postural control.



Marquer et al. (2014), *Ann Phys Rehabil Med* 57:67; Milne et al. (2020), *BMJ Open* 10:e040230.

PHYSICAL REHABILITATION · SYNTHESIS

Summary of the evidence

Intervention	Typical effect	Certainty
Coordinative training	↓ SARA ~2–3 pts; meaningful goal attainment	Moderate
Intensive inpatient rehab	↓ SARA; ↑ gait speed & ADL (RCT)	Moderate
Balance & gait training	↑ stability; falls reduction in some trials	Low–moderate
Exergames / VR	↓ ataxia; high engagement & home dose	Low–moderate
Treadmill / robotics	↑ gait parameters; limited data	Low
Torso weighting	Inconsistent; rarely durable	Very low

Bottom line: rehabilitation is the evidence-backed backbone — its effect is dose- and continuity-dependent.

Ilg et al. (2014), *Cerebellum* 13:248; Milne et al. (2020); Marquer et al. (2014).

PART III

Allied & supportive therapies

Protecting independence, communication and safety — where quality of life is won or lost.

ALLIED & SUPPORTIVE THERAPIES

Occupational therapy, ADL and assistive technology

Occupational therapy goals

Independence in activities of daily living

Energy conservation & fatigue management

Task adaptation & upper-limb strategies

Home-safety assessment

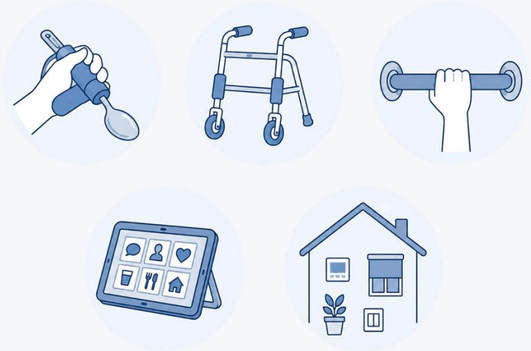
Assistive technology & environment

Adapted utensils & writing aids

Stable mobility aids (e.g. weighted walkers)

Grab rails & home modification

Communication & environmental controls



Combined **intensive OT + physiotherapy** outperforms OT alone — the disciplines are synergistic, not additive.

de Silva et al. (2019), *Orphanet J Rare Dis* 14:51; Miyai et al. (2012), *Neurorehabil Neural Repair* 26:515.

ALLIED & SUPPORTIVE THERAPIES

Speech therapy for ataxic dysarthria

The problem — a disorder of coordination

Imprecise consonants

Irregular articulatory breakdown

Scanning, abnormal prosody

Variable rate & loudness

→ reduced intelligibility and social participation

Under-studied but recommended: intensive and biofeedback-based speech protocols are under active evaluation.

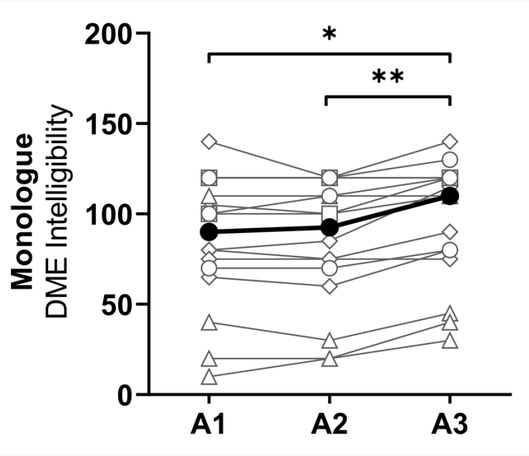
Speech-therapy approaches

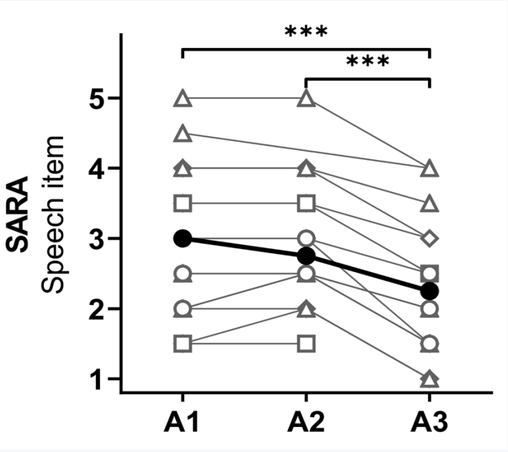
Rate control & pacing

Breath support & phonation

Prosody & intelligibility strategies

Biofeedback; delivered at intensity





de Silva et al. (2019), *Orphanet J Rare Dis* 14:51; Vogel et al. (2022), *Ann Clin Transl Neurol* 9:1310.

ALLIED & SUPPORTIVE THERAPIES

Swallowing and dysphagia management

> Dysphagia is common in progressive ataxia, and **aspiration pneumonia is a leading cause of death** — swallowing is a safety issue, not a comfort one.

01
Assess
Clinical + Videofluoroscopic Swallow Study (VFSS) / Fibreoptic Endoscopic Evaluation of Swallowing (FEES)

02
Modify
Texture & fluid adaptation

03
Strategies
Posture & swallow manoeuvres

04
Monitor
Planned surveillance

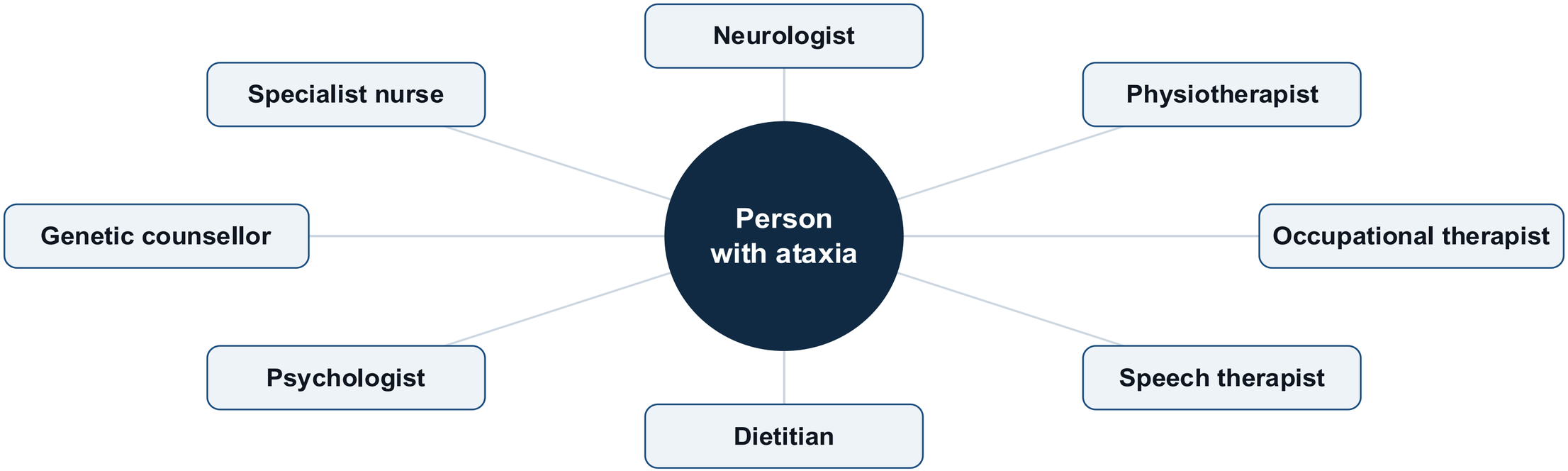
05
Enteral feeding
Discuss early, not in crisis

RED FLAGS Coughing on intake · Wet voice · Weight loss · Recurrent chest infections

de Silva et al. (2019), *Orphanet J Rare Dis* 14:51.

ALLIED & SUPPORTIVE THERAPIES

The multidisciplinary model of care



de Silva et al. (2019), *Orphanet J Rare Dis* 14:51.

PART IV

Non-invasive brain stimulation

Mechanisms, montages, dosing and the trial evidence — modulating the shared pathway directly.

NON-INVASIVE BRAIN STIMULATION

A taxonomy of non-invasive stimulation

Transcranial electrical (tES)

Subthreshold — shifts the probability of firing

tDCS
constant current — anodal ↑ / cathodal ↓ excitability

tACS
oscillating current — entrains rhythms

tRNS
random-noise current — stochastic facilitation

Transcranial magnetic (TMS)

Suprathreshold — can trigger action potentials

Single / paired-pulse
measurement — e.g. cerebellar-brain inhibition

rTMS
1 Hz suppresses · high-frequency facilitates

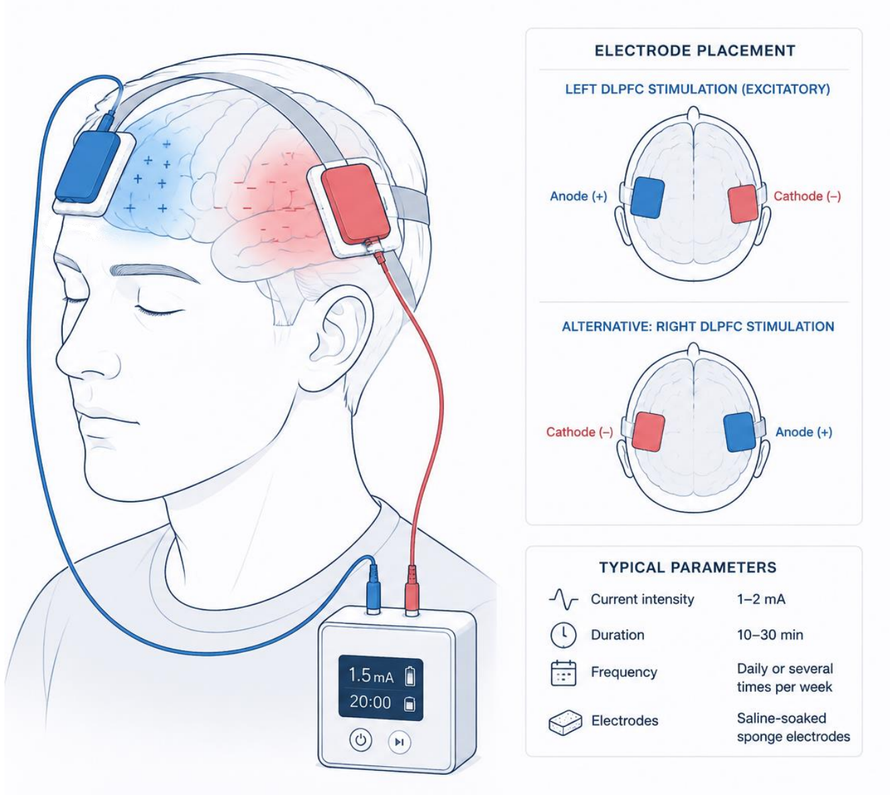
Theta-burst
iTBS facilitates · cTBS suppresses

tES modulates; TMS can drive — but both aim to renormalise cerebellar output.

Benussi, Pascual-Leone & Borroni (2020), *Int J Mol Sci* 21:1948; França et al. (2018), *Brain Stimul* 11:249.

TDCS · MECHANISM

tDCS biophysics: subthreshold modulation



TYPICAL PARAMETERS

Current intensity	1–2 mA
Duration	10–30 min
Frequency	Daily or several times per week
Electrodes	Saline-soaked sponge electrodes

Under the anode (+)

Depolarisation → ↑ **excitability** and firing probability

Under the cathode (−)

Hyperpolarisation → ↓ **excitability** (orientation-dependent)

Subthreshold — it modulates the probability of firing, never depolarizing. Lasting after-effects are **NMDA-dependent** (LTP/LTD-like plasticity).

Nitsche & Paulus (2000), *J Physiol* 527:633; Grimaldi et al. (2016), *Neuroscientist* 22:83.

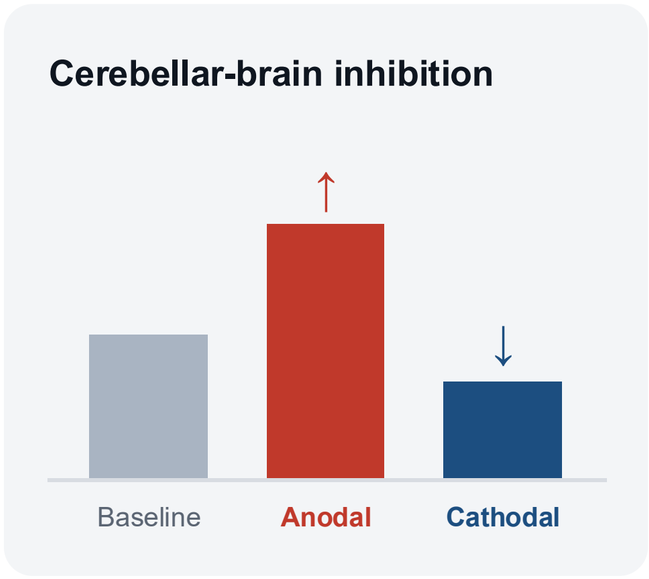
TDCS · MECHANISM

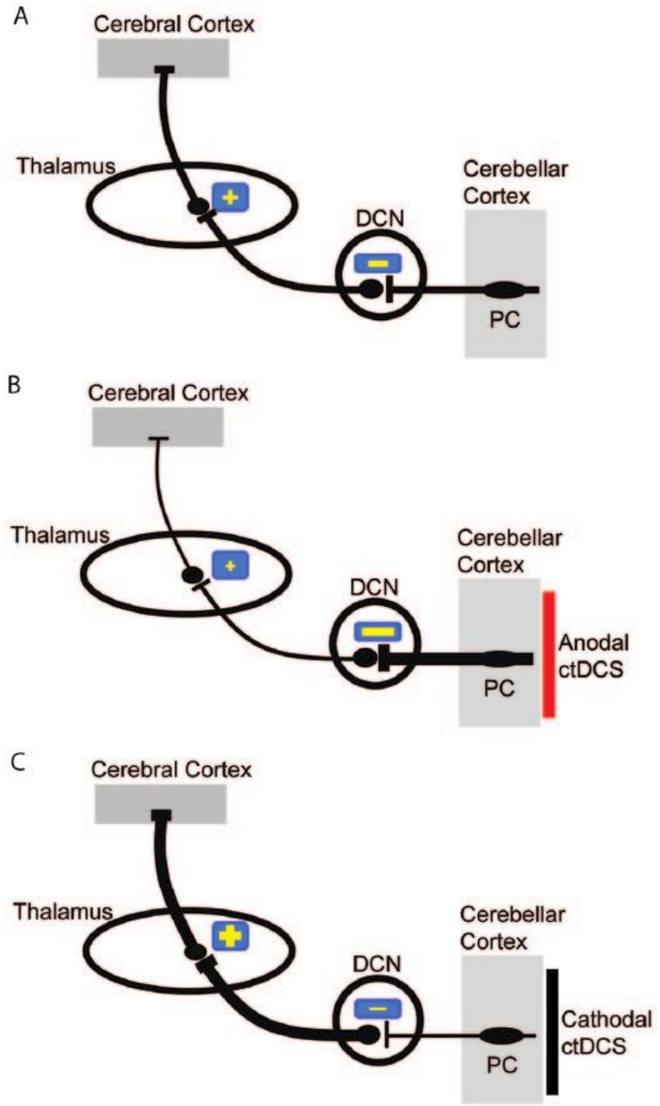
Polarity-specific control of cerebellar output

Cerebellar tDCS modulates **CBI in a polarity-specific way** :

- **Anodal** → ↑ cerebellar excitability → ↑ **CBI** (more Purkinje inhibition of the dentate)
- **Cathodal** → ↓ CBI

> In ataxia CBI is **reduced**; **anodal** tDCS aims to restore it — and CBI restoration paralleled clinical gains in several trials.

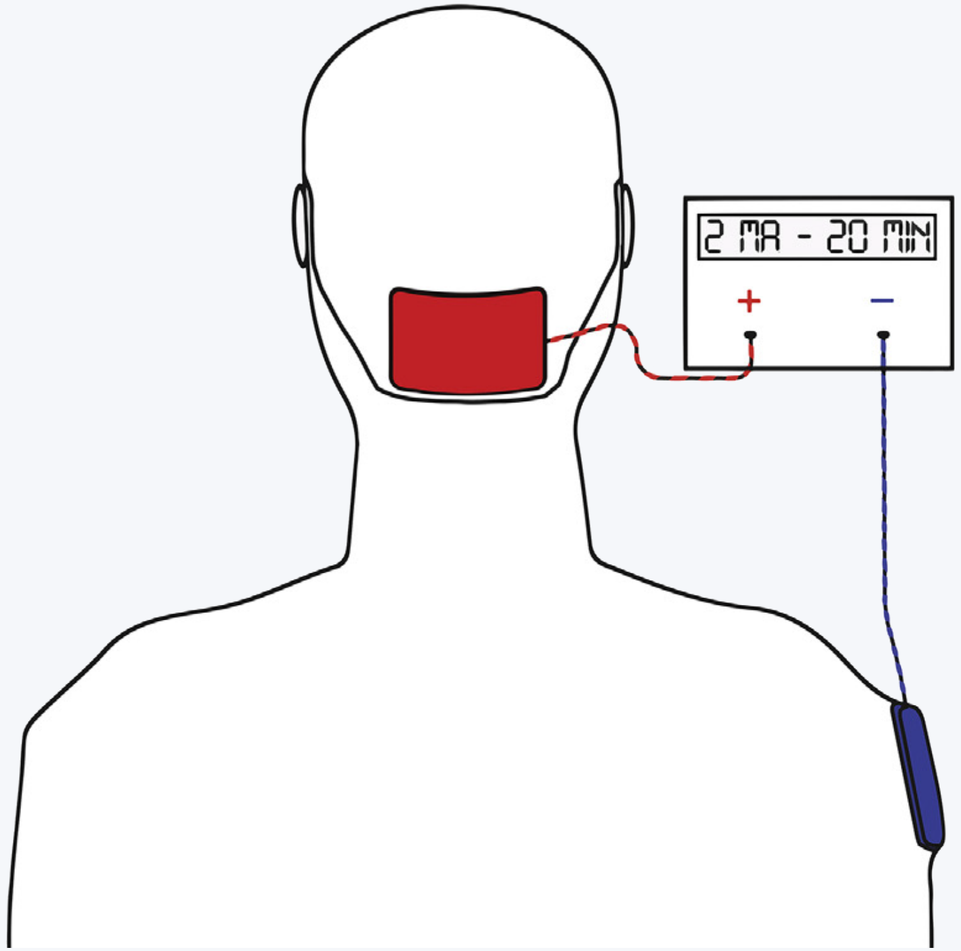




Galea et al. (2009), *J Neurosci* 29:9115; Benussi et al. (2017), *Brain Stimul* 10:242.

TDCS · MONTAGE & DOSING

The cerebellar tDCS montage



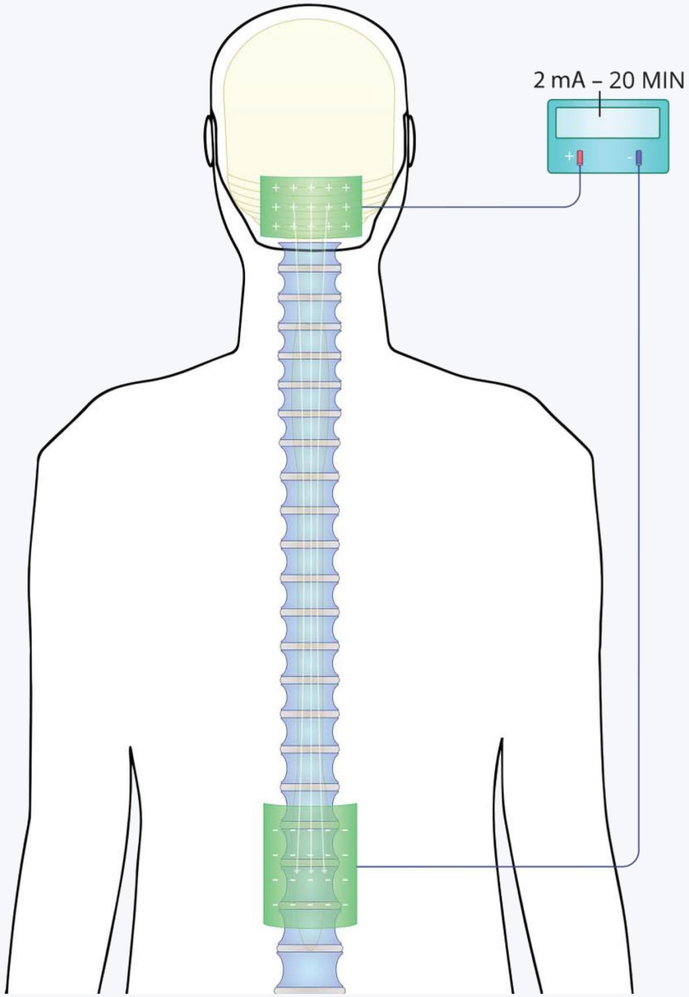
Anode (active)	**Cerebellum · midline, 2 cm below inion**
Cathode (reference)	**Buccinator or deltoid**
Electrode size	**5×5 – 5×7 cm (25–35 cm²)**
Intensity	**2 mA**
Duration	**20 min per session**
Current density	**≈ 0.06 mA/cm²**

Hemispheric targeting: anode ~1 cm below & 3 cm lateral to the inion.

Montage per Benussi et al. (2015, 2017); Maas et al. (2022); Grimaldi et al. (2016).

TDCS · MONTAGE & DOSING

The cerebello-spinal montage



The cathode moves from a distant reference to **over the spinal cord** — so the current engages spinal circuits as well as the cerebellum.

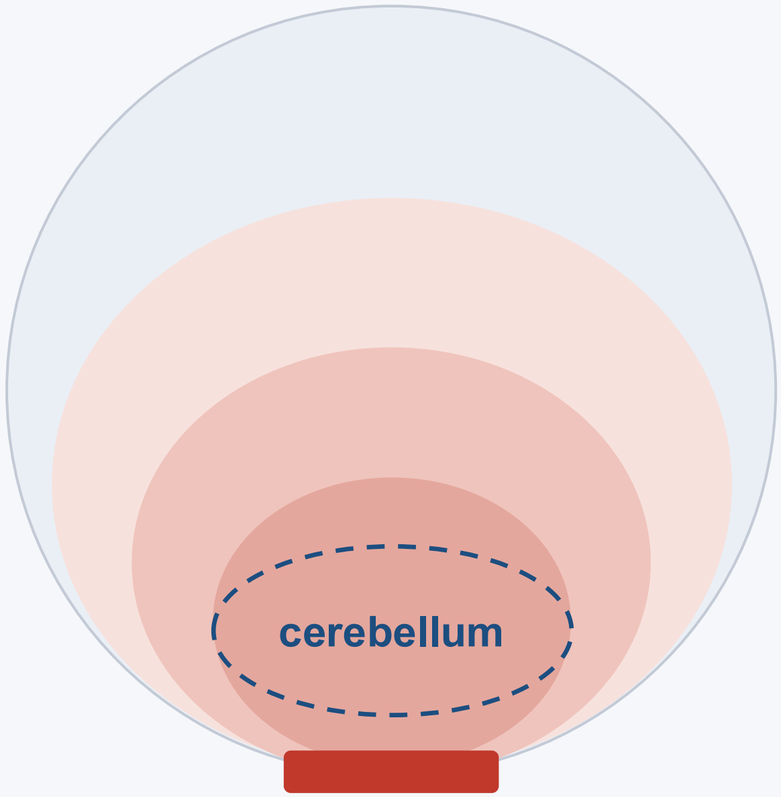
- Post-tDCS gains may be partly mediated by **spinal-cerebellar connectivity**
- Only a **spinal current component** engages spinal function directly

> Used in Benussi 2017 (2-week) and the 2018 crossover RCT — associated with **prolonged effects**.

Benussi et al. (2017), *Brain Stimul* 10:242; Benussi et al. (2018), *Neurology* 91:e1090.

TDCS · MONTAGE & DOSING

Dosing and current flow to the cerebellum



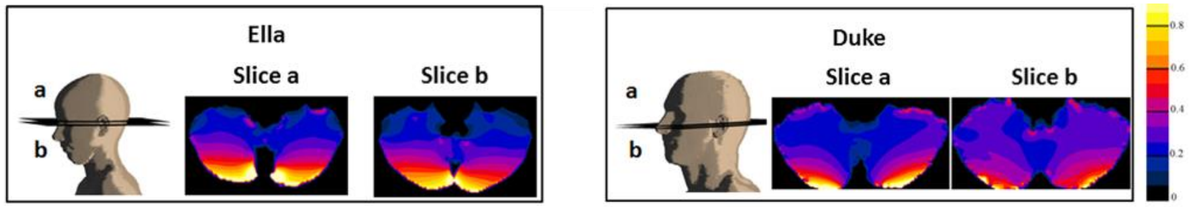
field falls off steeply with depth

Only a **fraction of scalp current** reaches the deep, folded cerebellum. Modelling shows the delivered field is highly **montage- and anatomy-dependent**.

WHAT CHANGES THE DELIVERED DOSE

- Skull thickness
- CSF layer
- Cerebellar atrophy
- Gyral folding
- Electrode montage

> **Anatomy matters** — a montage tuned in mixed cohorts may under-dose a specific anatomy, arguing for modelling-guided, individualised dosing.



Grimaldi et al. (2016), *Neuroscientist* 22:83; Maas et al. (2022), *Neurotherapeutics* 19:1259.

Single-session tDCS: the proof of concept

DESIGN

19 patients · single-session anodal cerebellar tDCS vs sham · double-blind, randomized

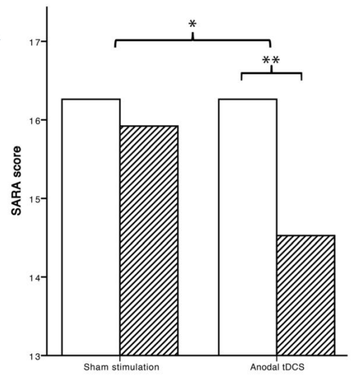
SIGNIFICANCE

All four measures improved vs sham — **P < 0.001**

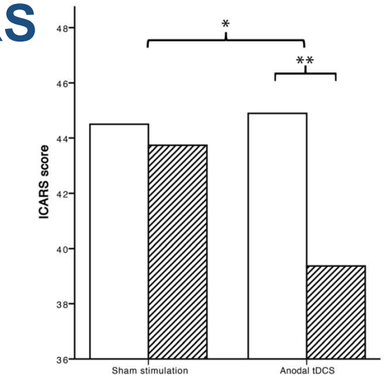
Transient — a single session; but proof the circuit is modifiable

Domains that improved

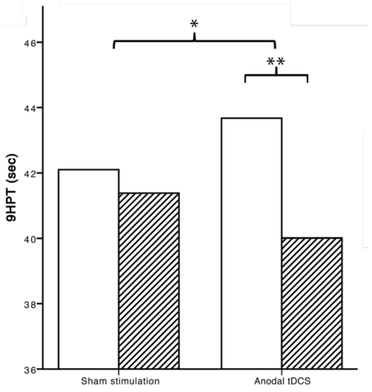
SARA



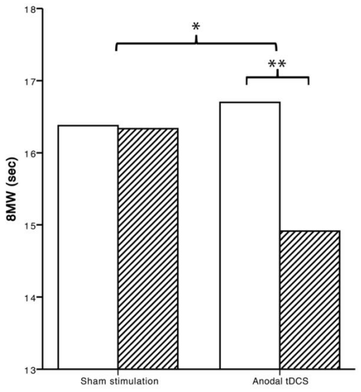
ICARS



9HPT



8MWT



Benussi et al. (2015), *Mov Disord* 30:1701.

Repeated tDCS: lasting effects and biomarker change

DESIGN

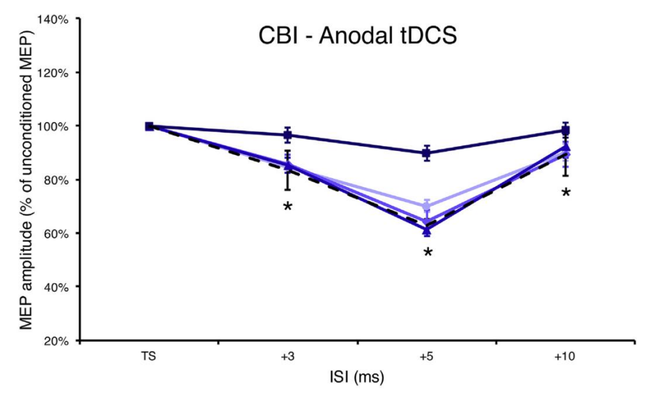
2 weeks of daily anodal cerebellar tDCS · mixed neurodegenerative ataxia

TARGET ENGAGEMENT

CBI restored — neurophysiology moved with the clinical gain, not just the score

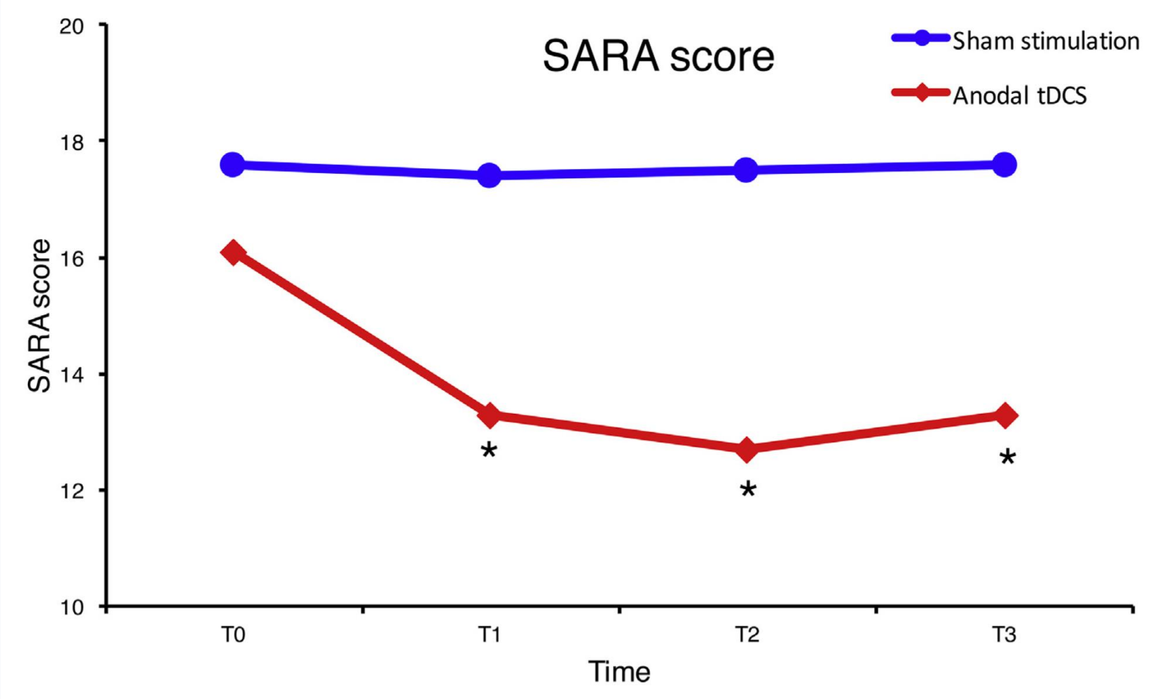
CBI

lower is better



Ataxia severity over time

lower is better

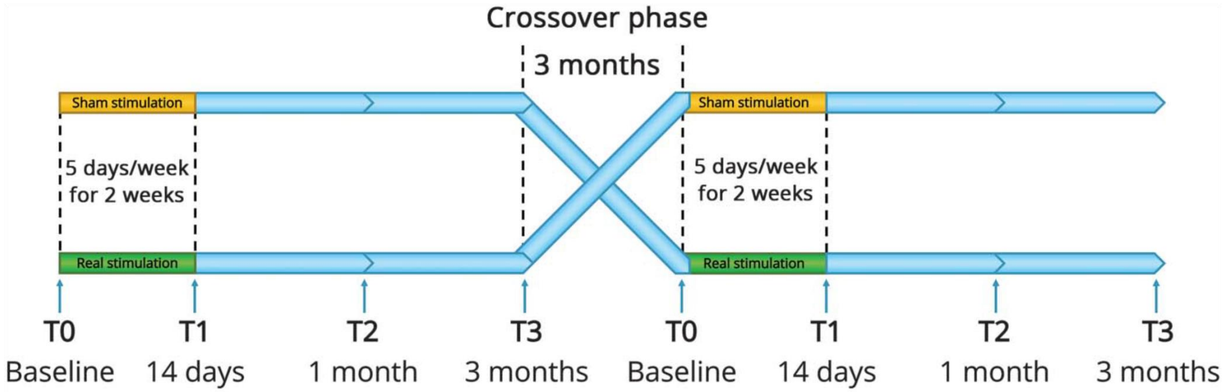


Benussi et al. (2017), *Brain Stimul* 10:242.

Cerebello-spinal tDCS: a crossover RCT

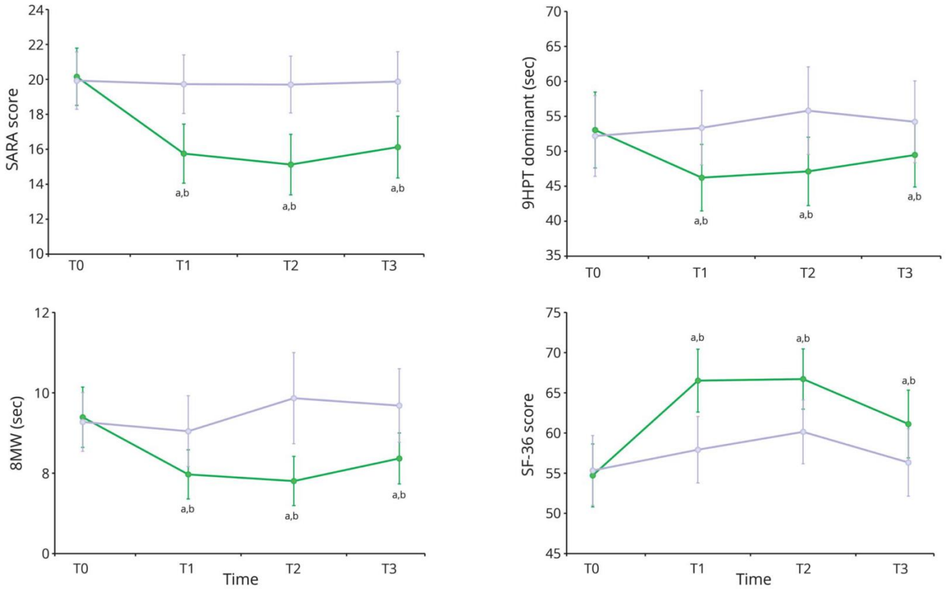
DESIGN

Randomized, double-blind, sham-controlled **crossover** · 2-week cerebello-spinal tDCS — each patient is their own control



Real > sham

- ↓ Ataxia scores (SARA, ICARS)
- ↑ Gait performance
- ↑ Upper-limb dexterity



Benussi et al. (2018), *Neurology* 91:e1090.

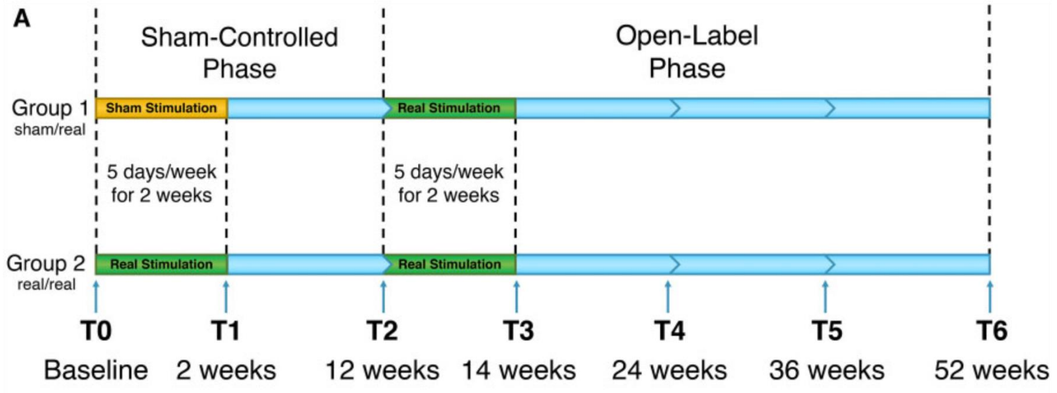
A larger trial: motor and cognitive outcomes

DESIGN

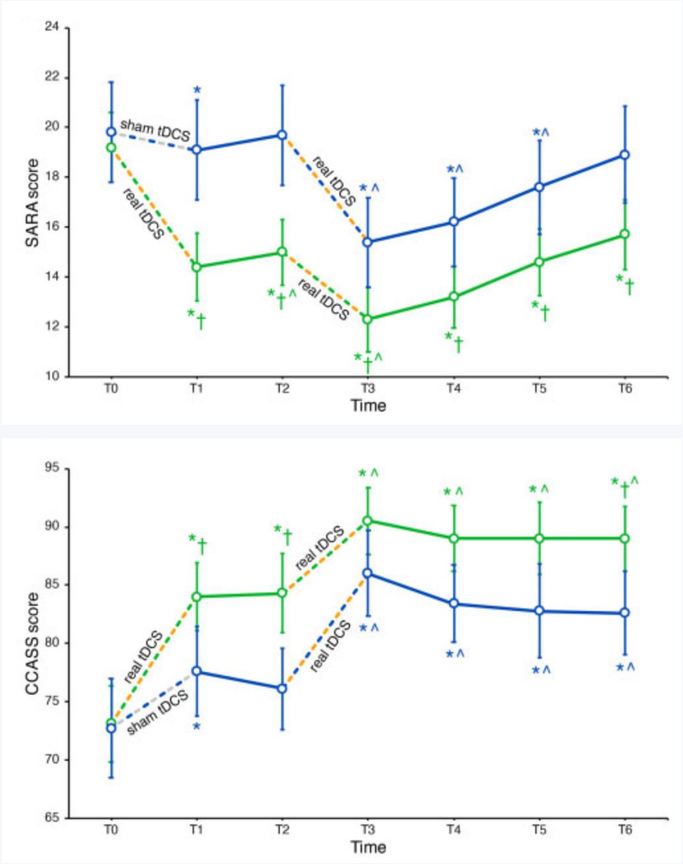
Larger randomized, double-blind, sham-controlled trial of cerebello-spinal tDCS · open-label extension

DUAL BENEFIT

Gains in **motor** and **cognitive** domains — consistent with cerebellar cognition



Add-on effect of a second course



Benussi et al. (2021), *Brain* 144:2310.

TDCS · EVIDENCE · MIXED FINDINGS

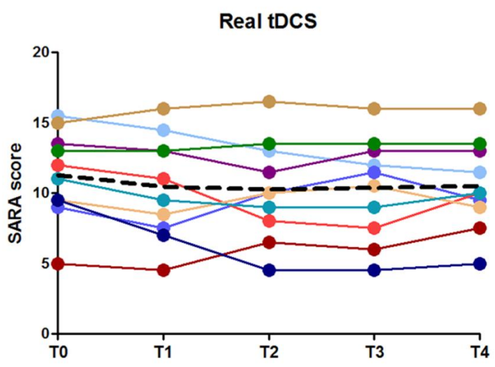
Response in genetically homogeneous cohorts

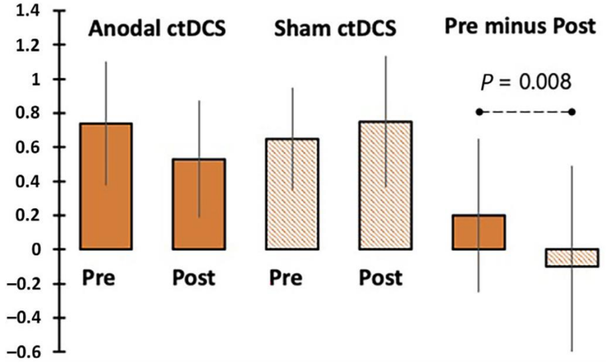
DESIGN

RCT of cerebellar tDCS in genetically homogeneous **SCA3** (n≈20), Benussi montage

RESULT

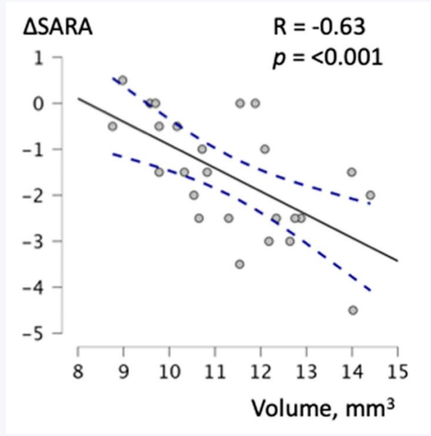
No group-level benefit on the primary outcome — unlike the mixed-etiology cohorts

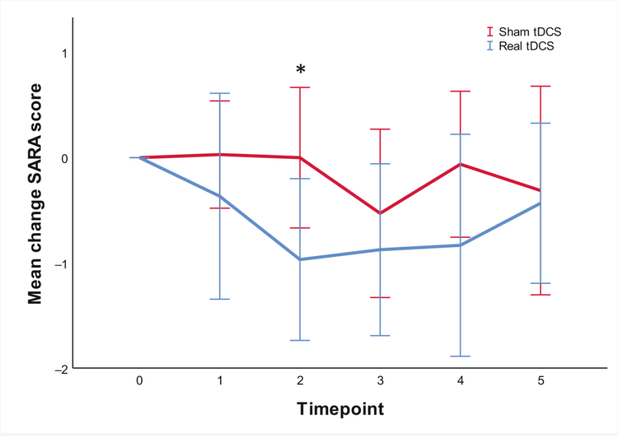




The broader lesson

- Marked **inter-individual variability** across trials (Maas 2022; Naeije 2023; Reumers 2025)
- Anatomy & disease stage shape the delivered dose & the response
- Genotype-specific, dose-individualised trials are the next step





Maas et al. (2022), *Neurotherapeutics* 19:1259; Naeije et al. (2025), *Clin Neurophysiol* 176:2110744; Reumers et al. (2025), *Mov Disord* 40:121.

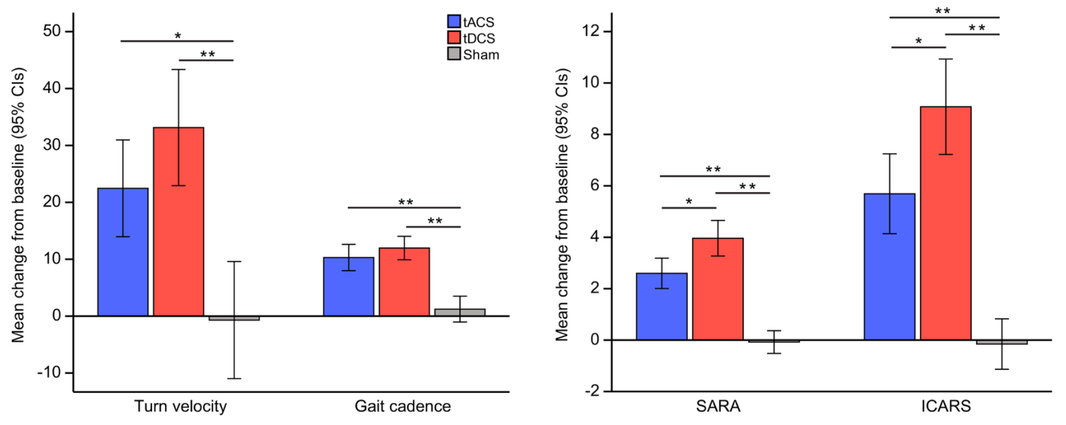
NON-INVASIVE BRAIN STIMULATION · EMERGING TES

Beyond tDCS: tACS and tRNS

tACS

alternating current — entrains oscillations

Can target **pathological rhythms**.



First head-to-head RCT

Cerebellar tACS vs tDCS vs sham in neurodegenerative ataxia — triple-crossover, wearable-sensor outcomes (Libri 2024)

tRNS

random noise — stochastic facilitation

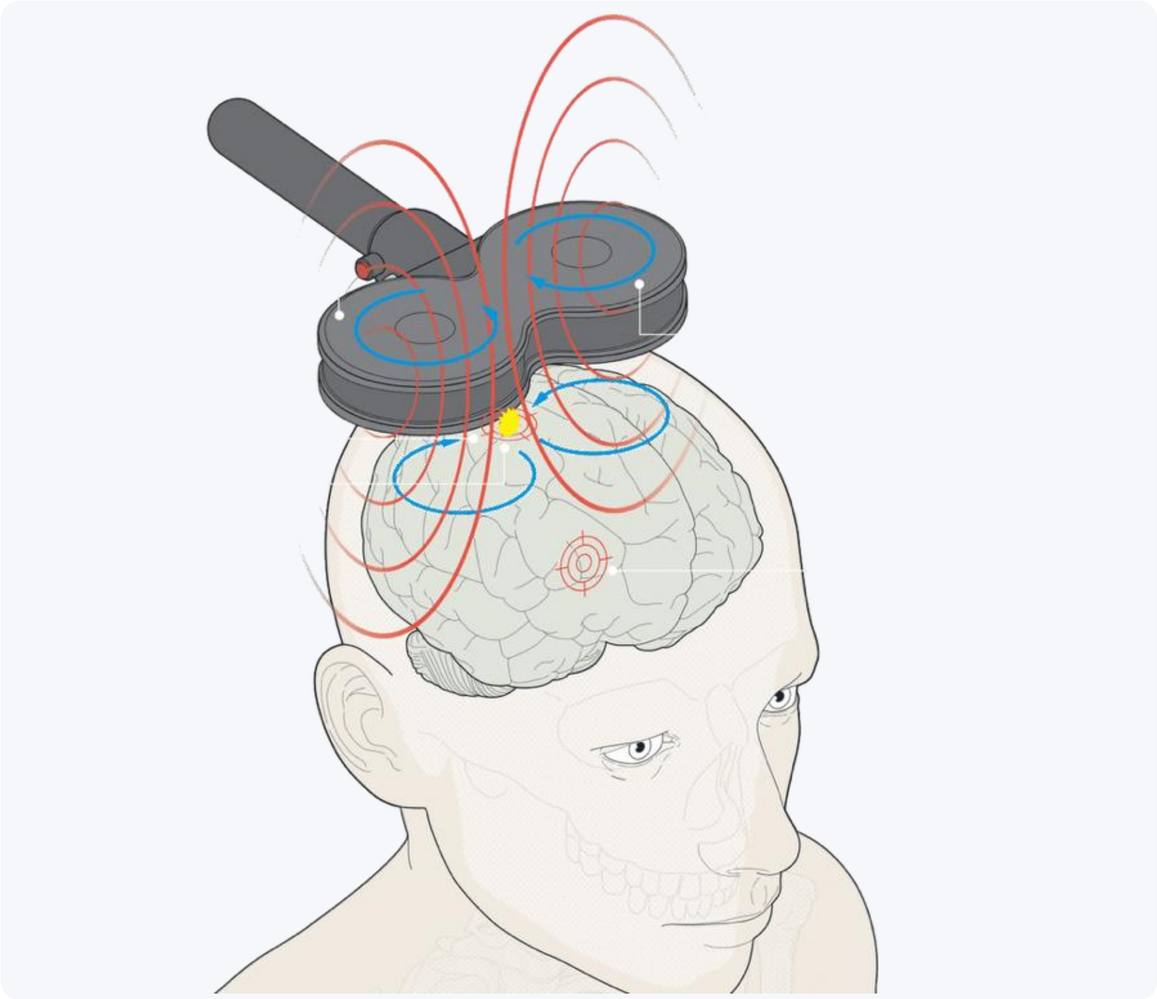
Random-noise current can raise cortical excitability through **stochastic resonance**, potentially amplifying weak signals.

Ataxia evidence: absent

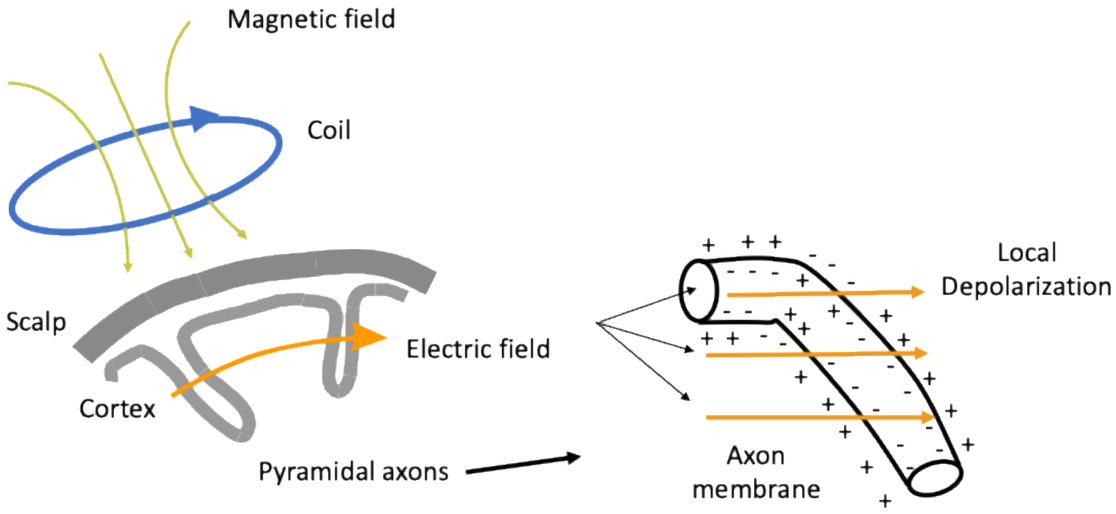
Benussi, Pascual-Leone & Borroni (2020), *Int J Mol Sci* 21:1948; Libri et al. (2024), *Cerebellum* 23:570.

TMS · MECHANISM

TMS biophysics: suprathreshold stimulation



- **Suprathreshold** — can trigger action potentials, not just bias firing
- **Focal but depth-limited** — a double-cone coil is used to reach the cerebellum
- **Single pulse measures** (e.g. CBI); **repetitive trains** induce plasticity



Barker et al. (1985), *Lancet* 1:1106; França et al. (2018), *Brain Stimul* 11:249.

TMS · PROTOCOLS

rTMS and patterned protocols

Low-frequency

≈ 1 Hz

↓ **suppresses** (LTD-like)

High-frequency

5 – 20 Hz

↑ **facilitates** (LTP-like)

Theta-burst

3 pulses @ 50 Hz, every 200 ms

intermittent facilitates · continuous suppresses

> For a failing cerebellum the usual aim is to **boost output,** favouring facilitatory protocols, but direction depends on the pathology.

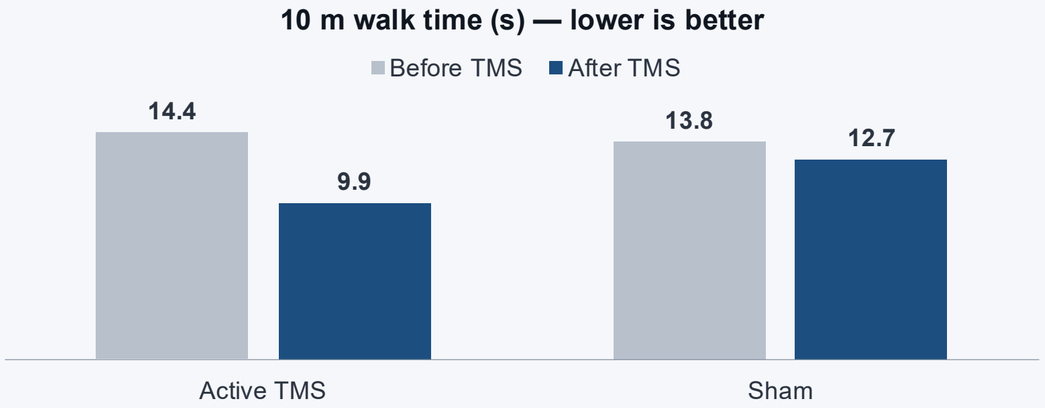
Huang et al. (2005), *Neuron* 45:201 (TBS); França et al. (2018), *Brain Stimul* 11:249.

TMS · EVIDENCE

Cerebellar rTMS: the trial evidence

Shiga 2002 RCT

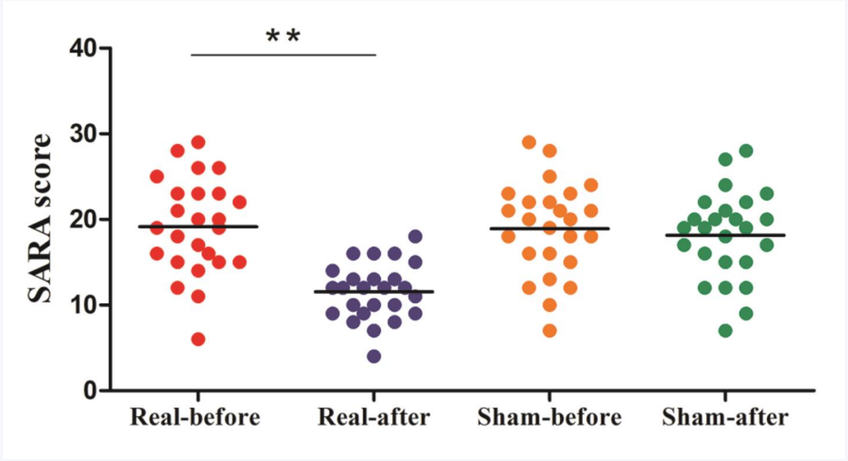
Repeated cerebellar TMS **alleviated truncal ataxia** in spinocerebellar degeneration.



Randomized, double-blind, sham-controlled.

Song 2020 RCT

Cerebellar rTMS in **MSA** improved SARA and, on TMS-EEG, modulated **cerebello-frontal plasticity**.



Randomized, double-blind, sham-controlled.

> rTMS trials are **fewer and smaller** than the tDCS set — but the direction of effect agrees.

Shiga et al. (2002), *J Neurol Neurosurg Psychiatry* 72:124; Song et al. (2020), *Aging* 12:20611.

NON-INVASIVE BRAIN STIMULATION · COMPARISON

tDCS versus rTMS

	tDCS	rTMS
Mechanism	Subthreshold — modulates firing	Suprathreshold — can drive firing
Ataxia evidence	**Larger** — several RCTs	Smaller — fewer, small trials
Focality	Diffuse	Focal
Cost & portability	**Low** — portable, home-capable	High — clinic-based
Tolerability	Very good (tingling, itch)	Good (scalp discomfort; rare seizure)
Control variable	Polarity (anodal / cathodal)	Frequency / pattern

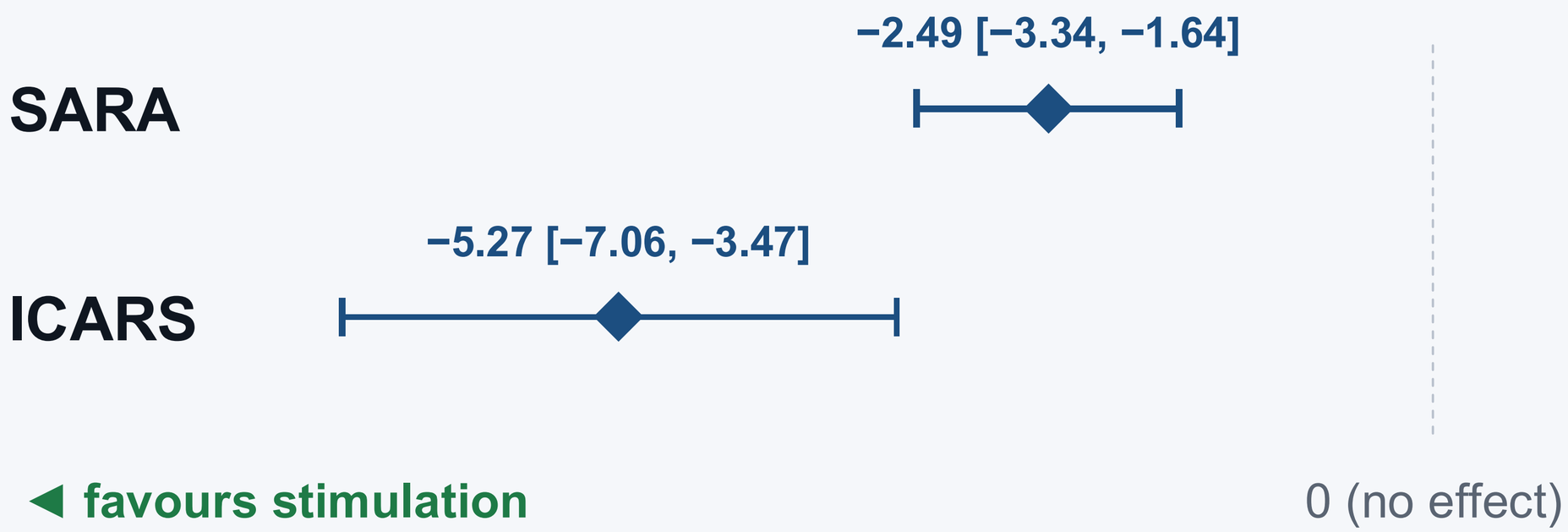
> Meta-analyses find **both reduce SARA and ICARS**, with no clear superiority of one modality.

Matsugi et al. (2024), *Mov Disord Clin Pract* 11:1323; Benussi et al. (2020), *Int J Mol Sci* 21:1948.

NON-INVASIVE BRAIN STIMULATION · SYNTHESIS

Meta-analytic evidence

Pooled effect vs control — negative favours stimulation (Matsugi 2024, 17 RCTs)



Read with caution: serious risk of bias, low certainty, high heterogeneity — the effect is real, but the precise size may change.

Matsugi et al. (2024), *Mov Disord Clin Pract* 11:1323.

PART V

Horizon & synthesis

Combination therapies, invasive options, the near future, and one integrated pathway that closes the loop.

NON-INVASIVE BRAIN STIMULATION · INTEGRATION

Combining stimulation with rehabilitation

PRIME

Stimulation

Raises cerebellar excitability, normalises CBI — opens a plasticity window

→

TRAIN

Intensive training

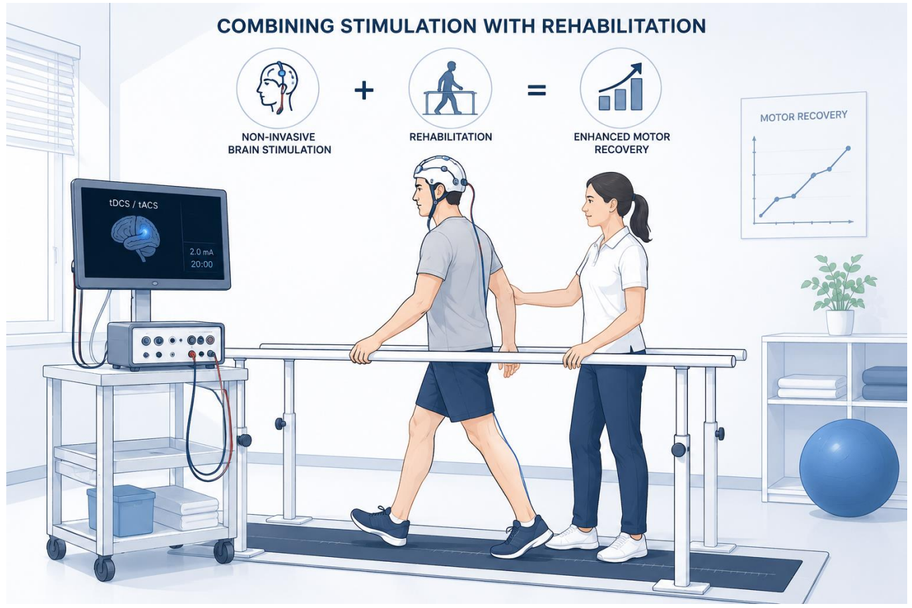
Drives task-specific coordinative learning into the primed circuit

→

CONSOLIDATE

Continued practice

Retains and compounds the gain over time



> The likely future is **integrated stimulation + intensive training** — not either alone. Evidence is early, but the rationale and consensus both point here.

Ilg et al. (2014), *Cerebellum* 13:248; Benussi et al. (2020), *Int J Mol Sci* 21:1948.

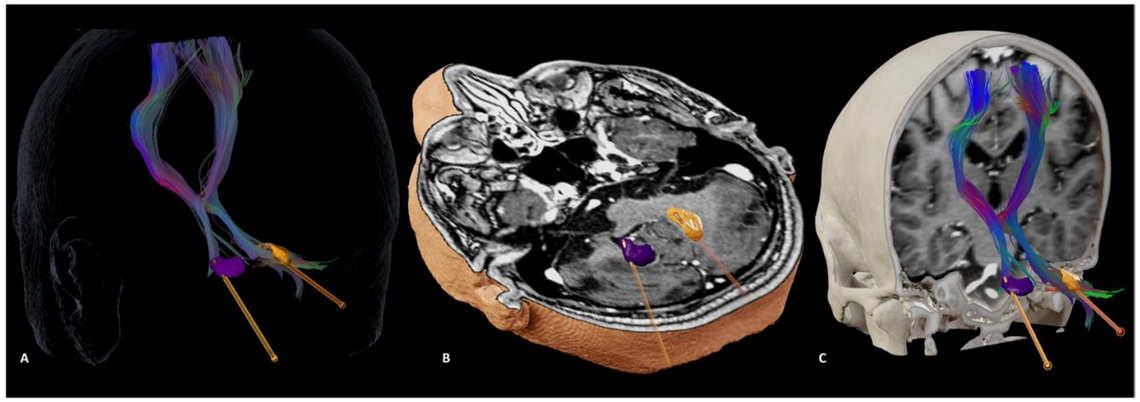
HORIZON & SYNTHESIS

Invasive neuromodulation

Experimental in ataxia

Small case series and pilots — not standard care.

Non-invasive stimulation reaches overlapping circuits without surgery — a major part of its appeal.



Dentate nucleus DBS

Investigational — directly targets cerebellar output

Thalamic (VIM) DBS

Mainly for the ataxic **tremor** component

Randomised double-blind crossover pilot · n = 5 (SCA3 / post-lesion ataxia)

Variable	Baseline	Active DN DBS	Sham DN DBS	P value*
SARA	10.7 ± 3.7	8.6 ± 3.6	10.1 ± 4.1	p = 0.223
FTMRS	21.1 ± 16.5	18.0 ± 17.2	22.2 ± 19.5	p = 0.039
WHOQOL-BREF	66.2 ± 18.4	74.7 ± 13.3	69.2 ± 22.8	p = 0.357
PGIC	–	3.2 ± 1.1	1.6 ± 0.9	p = 0.038

Active vs sham: tremor (FTMRS, p = 0.039) and global impression (PGIC, p = 0.038) improved; SARA ataxia change was not significant (p = 0.223). Safe and well tolerated — no serious adverse events.

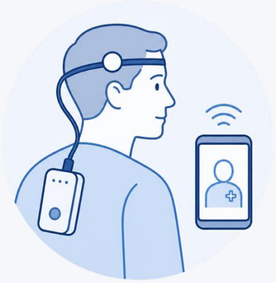
França et al. (2018), *Brain Stimul* 11:249; Mantovani et al. (2026), *Cerebellum* 25:59.; Cury et al. (2022), *Cerebellum* 21:861.

HORIZON & SYNTHESIS

Future directions

Home-based tES

Portable, high-dose, remote-supervised delivery



Individualised dosing

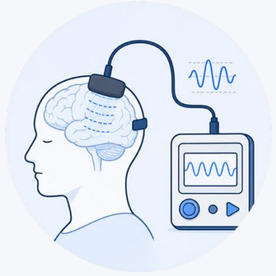
Modelling-guided, anatomy-aware current delivery

Closed-loop

Biomarker-guided — CBI, EEG targets

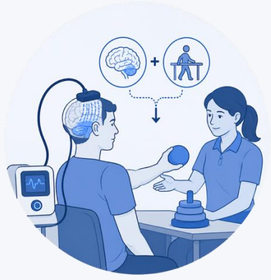
tACS for oscillations

Entraining or cancelling pathological rhythms



NIBS + rehabilitation

Prime-and-train combined protocols



Larger, standardised RCTs

Genotype-specific, common outcomes — the priority

Benussi et al. (2020), *Int J Mol Sci* 21:1948; Matsugi et al. (2024), *Mov Disord Clin Pract* 11:1323.

IN SUMMARY

Key conclusions

1. Hundreds of ataxias, one syndrome — and for **most, no disease-modifying therapy**
2. Non-pharmacological treatment acts on the **shared final common pathway** — etiology-agnostic
3. **Rehabilitation is the backbone** — benefit is dose- and continuity-dependent
4. **Cerebellar tDCS** has the strongest NIBS evidence — effects last ~3 months and track CBI
5. **Response is variable** — anatomy, stage & dose matter; treat early, individualise
6. The future is **integrated stimulation + intensive training**, proven in larger RCTs

AUDIENCE POLL

Which non-pharmacological approach do you think has the strongest randomised evidence in ataxia today?

- **A** Intensive coordinative physiotherapy
- **C** Cerebellar rTMS
- **B** Cerebellar tDCS
- **D** None has RCT-level evidence yet

AUDIENCE POLL

Which non-invasive brain stimulation approach has the strongest randomised evidence in ataxia?

A Cerebellar rTMS

C Cerebellart ACS

B Cerebellar tDCS

D Cerebellar tRNS

DISCUSSION

Thank you for your attention

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