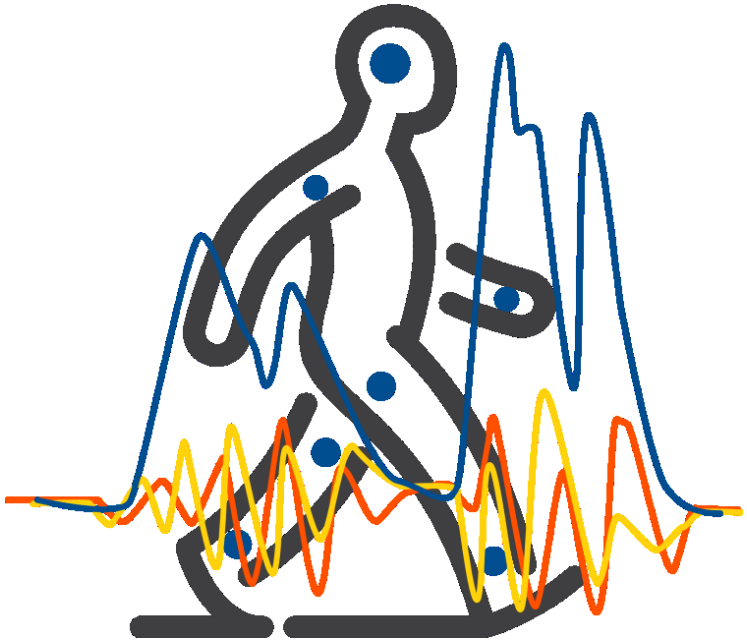
European Reference Network
for rare or low prevalence complex diseases
Network Neurological Diseases (ERN-RND)

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'
10. November 2020

Joint webinar series

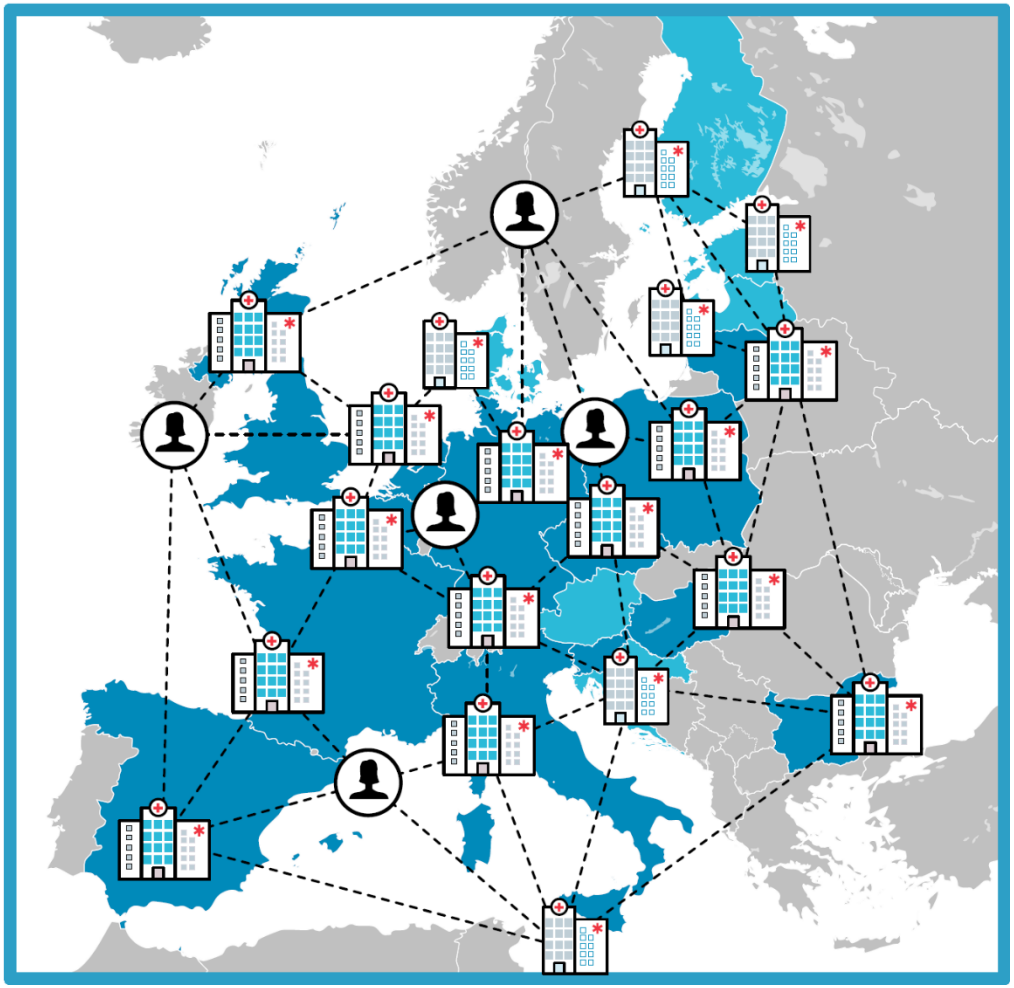


'Rehabilitation in ataxia: current evidence and practice'

by Ludger Schöls
Hertie Institute for Clinical Brain Research,
University of Tübingen, Germany

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: Ludger Schöls

Training:
- Medical Studies (MD): Universities of Bonn, Tübingen and Edinburgh
- Specialist training (Neurology): Ruhr-University Bochum, Germany
- Habilitation: Clinical and genetic characterization of hereditary ataxias

Current position: Full Professor of Clinical Neurogenetics, University of Tübingen

Other key positions/activities:
- Section head: Hertie-Institute for Clinical Brain Research, Tübingen
- Deputy Director, Dep of Neurology, University of Tübingen
- Speaker: Center for rare neurological diseases, University of Tübingen
- Group leader: German Center for Neurodegenerative Diseases (DZNE), Tübingen
- Clinical coordinator of the European Reference Network for Rare Neurological Diseases (ERN-RND)

Research focus:
- Neurogenetics: discovering genetic causes of neurological diseases & genotype-phenotype analyses
- Translational research: natural history studies, biomarker development & interventional trials.
  Disease modelling in iPSC-derived neuronal cell models
  In vitro and in vivo studies of innovative compounds

Webinar outline

- Introduction to cerebellar ataxias
- Studies on physical therapy
- Video-game based training
- Speech treatment
- Adapted physical activities
- Open questions

Learning objectives

By the end of this webinar you will:

- now various beneficial rehab strategies in ataxias
- be able to appraise effects of physical therapy, exergames and speech therapy
- understand factors that influence its success
- be aware of open questions in ataxia rehab

Background of participants

Your expertise in the field of ataxia:

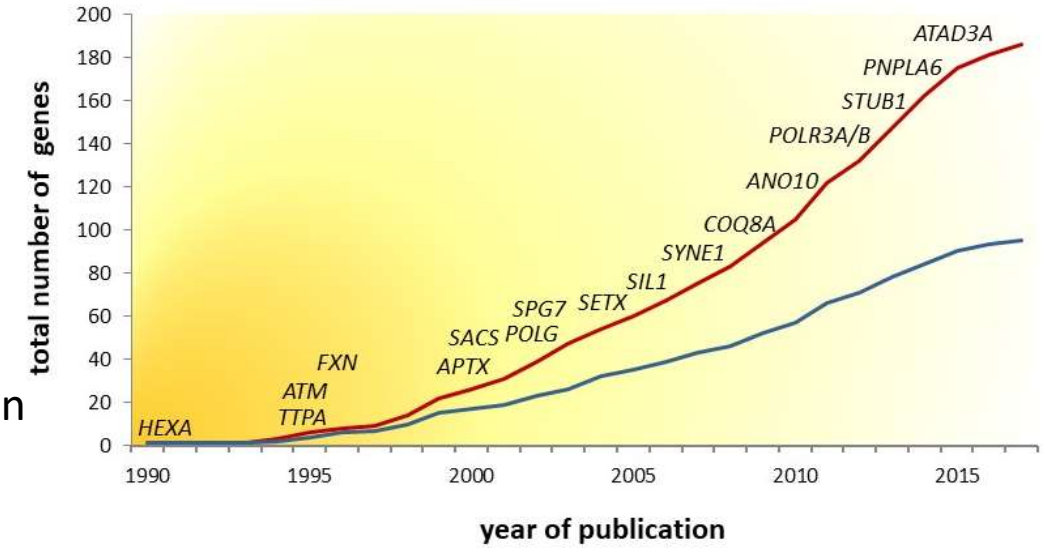
- Ataxia patient or patient advocate
- Physiotherapist
- Neurologist
- Pediatrician
- Others

Ataxia

- Greek (ἀ-ταξία): Out of order
- Key problem: Lack in coordination due to problems in precision and timing of movements
- Affects:
  - Gait
  - Stance
  - Dexterity
  - Articulation
  - Eye movement coordination

Ataxia

- Many causes:
  - Vascular: Cerebellar stroke
  - Autoimmune: e.g. Multiple sclerosis, SREAT, …
  - Inflammatory: Viral cerebellitis
  - Metabolic: e.g. Vitamin B12, Wilson
  - Toxic: e.g. Alcohol, drugs
  - Tumor
  - Neurodegenerative: MSA-C
  - Hereditary:
    - Many SCA and ARCA genes
    - Numbers still increasing



Autosomal recessive ataxia genes

Synofzik, …, Schöls Neuron 2019

Cerebellar ataxias

Clinical features

- Pure cerebellar ataxia
- Ataxia Plus Syndromes:
  - Non-cerebellar manifestations frequently complicate movement disorder
  - need to be considered in therapy
    - Spasticity
    - Peripheral neuropathy / afferent deficits
    - Parkinsonism
    - Dystonia
    - Tremor
    - Myoclonus
    - …

Neuronal structures

- Purkinje cells / cerebellar cortex:

  e.g. SCA6
- Cerebellar nuclei:

  e.g. SCA3
- Spinocerebellar afferent tracts:

  e.g. Friedreich's ataxia
- Olivo-ponto cerebellar affection:

  e.g. MSA-C
- Basal ganglia: e.g. MSA, SCA3

Treatment of ataxias

Ataxia

- Emerging, mechanism-based, causative treatment approaches
- Symptomatic treatment of ataxia:
  - 4-aminopyridine, riluzole?, …
  - Non-invasive cerebellar stimulation?
  - Prism for diplopia
  - Exercise & rehabilitation

Non-cerebellar symptoms

Don’t miss to treat:

- Spasticity
- Dystonia
- Parkinsonism
- Restless legs
- Dysphagia
- Neurogenic bladder disturbances
- Dysaethesia
- Cramps

Key questions

- Can patients with cerebellar ataxias improve their performance by training?
  - Is motor learning still possible if the degenerative process affects the cerebellum as a whole?
  - Which structures are involved / need to be preserved?
  - How does on optimal training concept look like?
- How to measure training effects?
  - Ataxia scores: SARA, ICARS
  - Berg balance scale
  - Falls
  - Goal attainment score
  - ADL, …

Physical therapy in ataxia

- Which therapy do you recommend in cerebellar ataxias?
  - Vojta
  - Bobath
  - Isometric training
  - Massage / relaxation
  - Falling strategies
  - Vibration
  - Hippotherapy
  - Aqua aerobics
  - Balance training
  - Coordinative training

Fields in rehabilitation

- **Physical therapy**
  - **Videogame-based training**
  - **Adapted physical activity**
- Occupational therapy
- Hippotherapy
- Aqua aerobics
- **Speech therapy**

"Table Tennis"

Evidence for physical therapy in ataxia

Randomized controlled trials

Author	Disease	Age (year, mean ± SD)	Number of subjects	Intervention	Protocol	Outcome measures	Main results	Follow-up
Miyai et al. [15] 2012	SCA6, SCA31, ICA	62.5 ± 1.7	42 (21 in each group)	Intensive rehabilitation focusing on coordination, balance and ADLs vs. delayed intervention	2 h of physical and occupational therapy on weekdays and 1 h on weekends for 4 weeks	SARA, FIM, gait speed, cadence, FAC and number of falls	Improvements in ataxia, gait speed, and ADLs	Yes (4–12-24 weeks)
Rodríguez-Díaz et al. [16] 2018	SCA2	39.52 ± 10.72 for intervention group; 38.78 ± 10.53 for control group	38 (19 in each group)	Neurorehabilitation therapy focusing on balance, coordination, and strengthening vs. no intervention	6 h of neurorehabilitation per day on weekdays for 24 weeks	SARA, non-ataxia symptoms and saccadic eye movement variables	Improvements in motor symptoms, especially gait, postural stability, and coordination	No
Bunn et al. [17] 2015	SCA6	60.2 ± 10.5 for intervention group; 58.3 ± 14.5 for control group	12 (6 in each group)	Home balance exercises in front of optokinetic stimuli vs. no intervention	15 min per session, 1 session per day, and 5 days per week for 4 weeks	SARA, standing sway, FIM, FBS, EQ-5D, EQ-VAS, ABC, FSS, VASf	- Training is proven feasible - No adverse events reported	No

He et al. J Neurol 2020

Randomized controlled trial

Clinical Research Articles

Cerebellar Ataxia Rehabilitation Trial in Degenerative Cerebellar Diseases

Neurorehabilitation and Neural Repair
26(5) 515–522

DOI: 10.1177/1545968311425918
http://nnr.sagepub.com
SAGE

Ichiro Miyai, MD, PhD[1], Mizuki Ito, MD, PhD[2], Noriaki Hattori, MD, PhD[1,3], Masahito Mihara, MD, PhD[1], Megumi Hatakenaka, MD, PhD[1], Hajime Yagura, MD, PhD[1], Gen Sobue, MD, PhD[2], and Masatoyo Nishizawa[4], for the Cerebellar Ataxia Rehabilitation Trialists Collaboration

- 42 patients (40-82 years) with pure cerebellar ataxia
- Delayed onset design
- 4 weeks inpatient training: 2h coordinative training on working days + 1 h at weekends
- Immediate group with significant improvement in SARA, gait speed + ADL

Table 3. Long-Term Changes of Outcome Measures After 4-Week Inpatient Rehabilitation in Patients With Degenerative Cerebellar Diseases[a]

	Preintervention	Postintervention	4 Weeks	12 Weeks	24 Weeks	*P* Value
SARA	11.7 (0.6)	9.6 (0.6)***	10.3 (0.6)***	10.7 (0.6)*	11.3 (0.7)	<.001
FIM total	119.3 (0.9)	120.6 (0.8)***	120.2 (0.8)**	119.7 (0.9)	119.2 (1.3)	=.001
FIM motor	85.2 (0.8)	86.4 (0.7)***	86.0 (0.7)**	85.7 (0.8)	85.1 (1.2)	<.001
FIM cognitive	34.1 (0.3)	34.2 (0.3)	34.2 (0.3)	34.0 (0.3)	34.0 (0.3)	NS
Gait speed (m/s)	0.861 (0.050)	0.991 (0.055)***	0.979 (0.055)***	0.963 (0.057)**	0.927 (0.054)	$F(4, 156)= 10.8, <.001$
Normalized gait speed	1.000 (0)	1.171 (0.034)***	1.156 (0.030)***	1.151 (0.040)**	1.098 (0.032)*	$F(4, 156)= 10.2, <.001$
Cadence (steps/min)	110.0 (4.3)	113.2 (4.4)	111.8 (4.4)	111.8 (4.4)	110.8 (4.5)	NS
FAC	3.9 (0.2)	4.0 (0.2)**	4.0 (0.2)*	4.1 (0.2)**	4.0 (0.2)	<.01
Falls (times per 4 weeks)	1.5 (0.4)	0.3 (0.1)**	0.8 (0.4)	1.1 (0.4)	1.4 (0.5)	<.005

Abbreviations: SARA, Scale for the Assessment and Rating of Ataxia FIM, Functional Independence Measure; FAC, Functional Ambulation Category; NS, not

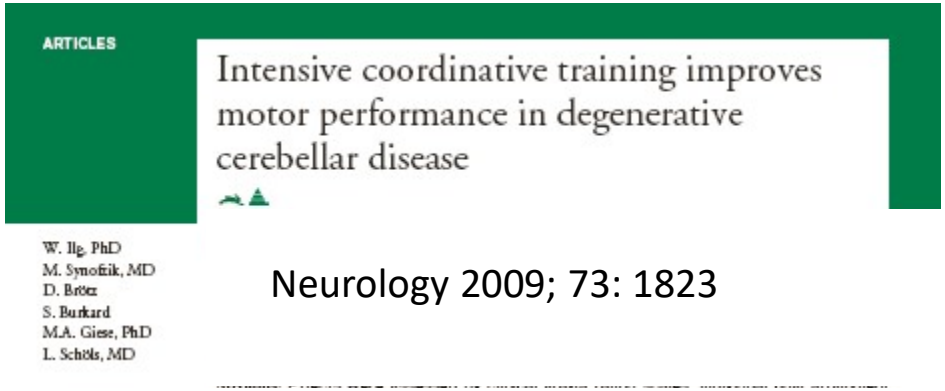
Evidence for physical therapy in ataxia

Non-Randomized controlled trials

Author	Type of study	Disease	Age (year, mean ± SD)	Number of subjects	Intervention	Protocol	Outcome measures	Main results
Ilg et al. [22, 23] 2009 + 2010	Prospective study	SCA2, SCA6, ICA, FA, ADCA, SANDO, ICA with SN	61.4 ± 11.2	16	Coordinative training	4-week intensive coordinative training (3 1-h sessions per week) followed by home exercises (1 h per day)	SARA, ICARS, BBS, GAS, gait parameters. static balance test, dynamic balance task	Improvements in motor performance and ataxia symptoms
Keller et al. [24] 2014	Prospective study	SCA3, SCA5, SCA6, SCA8, SCA17, ADCA, Sporadic cerebellar ataxia	52.4 ± 11.5	14	Individualized home-based exercise program	For most participants: ≥ 3 days per week for 6 weeks	ICARS, DGI, TUG, FR, ABC, static standing balance, walking speed, stride length	- Improvements in gait and balance - No falls
Fonteyn et al. [26] 2014	Prospective study	SCA6, SCA3, SAOA	61.4 ± 5.7	10	Gait adaptability training	1 h per session, and a total of 10 sessions over 5 weeks	SARA, 10MWT, TUG, BBS, the obstacle subtest of EFAP, ABC	Improvements in obstacle avoidance capacity and dynamic stability

He et al. J Neurol 2020

Active coordinative training


ARTICLES

Intensive coordinative training improves motor performance in degenerative cerebellar disease

W. Ilg, PhD
M. Synofzik, MD
D. Brötz
S. Burkard
M.A. Giese, PhD
L. Schöls, MD

Neurology 2009; 73: 1823

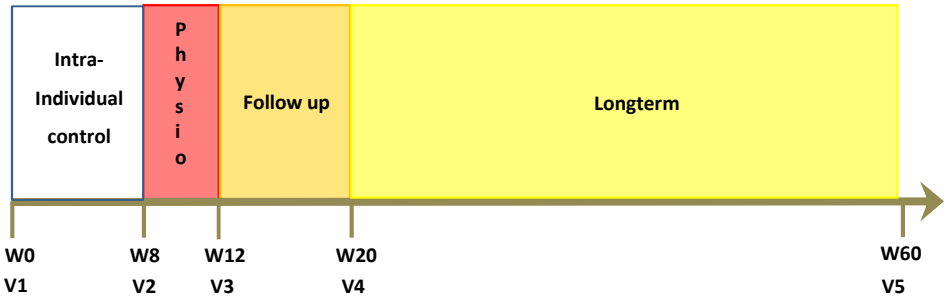
Long-Term Effects of Coordinative Training in Degenerative Cerebellar Disease

Winfried Ilg, PhD,[1] Doris Brötz, PT,[2] Susanne Burkard, PT,[3] Martin A. Giese, PhD,[1] Ludger Schöls, MD,[4*] and Matthis Synofzik, MD[4]

Mov Dis 2010; 25: 2239

Concept by Doris Brötz (Tübingen):

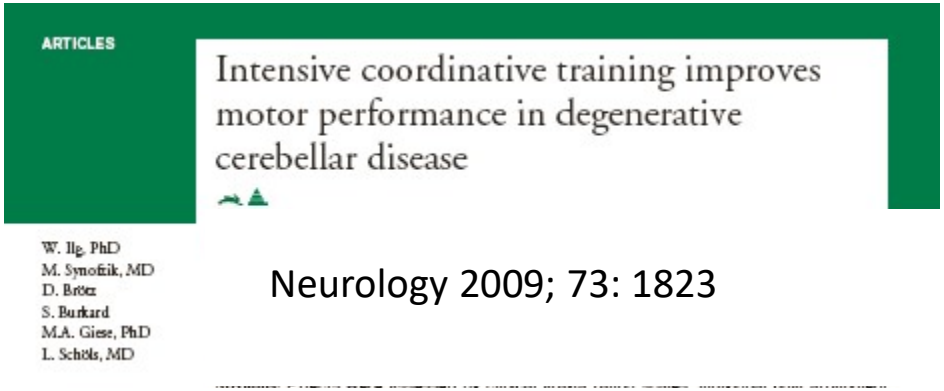
- Active release of „fixed“ movement patterns
- Training of static balance
- Training of dynamic balance
- Whole body movements
- Falling strategies and steps to prevent falling
- Movements to treat and prevent contractures
- Rather few exercises but frequent repetitions



Intervention:

- 16 patients (40 – 79 years)
- 4 weeks course: 3 x physical therapy / week = 12 x physical therapy per patient

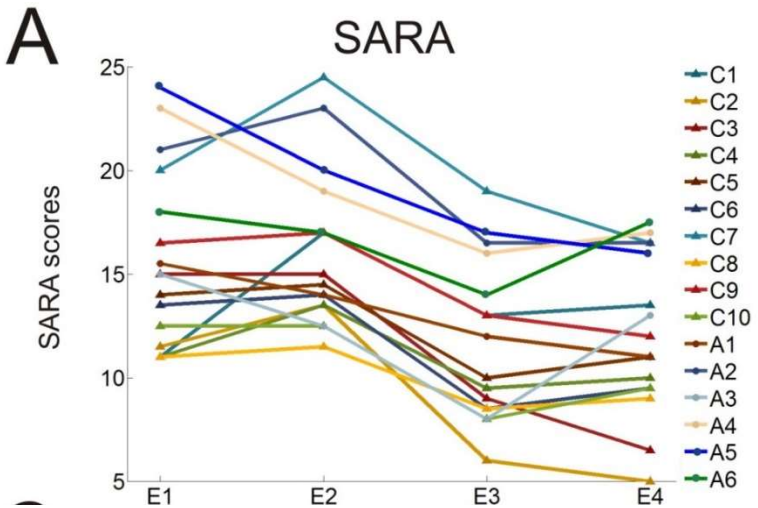
Active coordinative training


ARTICLES

Intensive coordinative training improves motor performance in degenerative cerebellar disease

W. Ilg, PhD
M. Synofzik, MD
D. Brötz
S. Burkard
M.A. Giese, PhD
L. Schöls, MD

Neurology 2009; 73: 1823



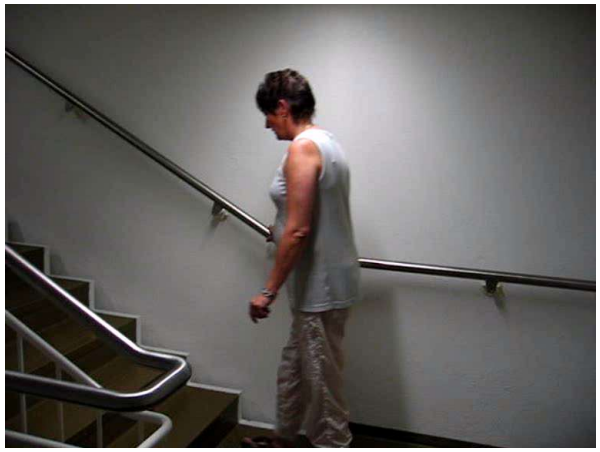
Results after 4 weeks of training

- Improvement of 5.2 SARA points
  = natural disease progression in 2–4 years
- Improvement also in
  - Digital movement recordings
  - Berg Balance Scale and
  - Goal attainment scale
- Persistent effect after 12 weeks
- Larger benefit in patients with cerebellar ataxia than afferent ataxia

Active coordinative training

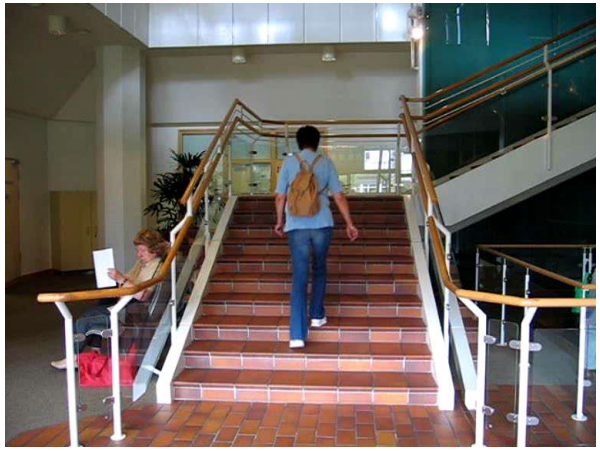
Pre





Post





Goal attainment score

ARTICLES

Intensive coordinative training improves motor performance in degenerative cerebellar disease

W. Ilg, PhD
M. Synofzik, MD
D. Brötz
S. Burkard
M.A. Giese, PhD
L. Schöls, MD

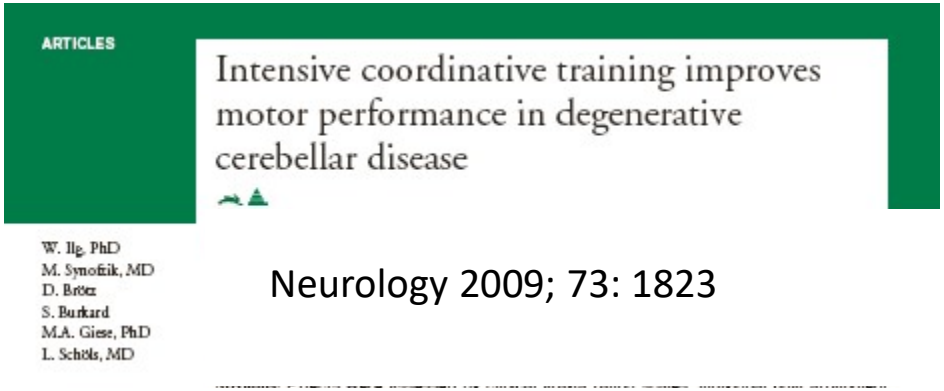
Neurology 2009; 73: 1823

Table 2 Example for a personally selected goal of the goal attainment score

Individual goal: Walking around a table with small distance without swaying	Score
The patient walks around the table mainly by touching the table	−2
The patient can walk around the table without touching the table most of the time	−1
The patient can walk around the table without touching the table	0
The patient can walk around the table without touching the table and is able to look around sometimes	+1
The patient can walk around the table without touching the table and is able to look around the whole time	+2

Patient	Goal	Score
C1	Walking on a narrow path (<50 cm)	2
C2	Walking up a staircase without using railway	2
C3	Reaching the mailbox in a distance of 600 m without using a walking aid	0
C4	Walking around a table with small distance without swaying	1
C5	Walking without a walking aid over a distance >10 m	1
C6	Walking over a distance of about 300 m without a walking aid or a helping person	2
C7	Walking over a distance of 50 m with a trolley, without bumping with the feet into it	1
C8	Walking free on a small staircase (3 steps) in an alternating way with a distance of 1 m to the railway	−1
C9	Walking with a trolley over a distance of 50 m	0
C10	Walking without a walking aid over a distance of about 100 m	0

Digital movement recording


ARTICLES

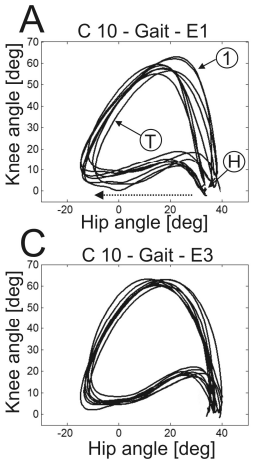
Intensive coordinative training improves motor performance in degenerative cerebellar disease

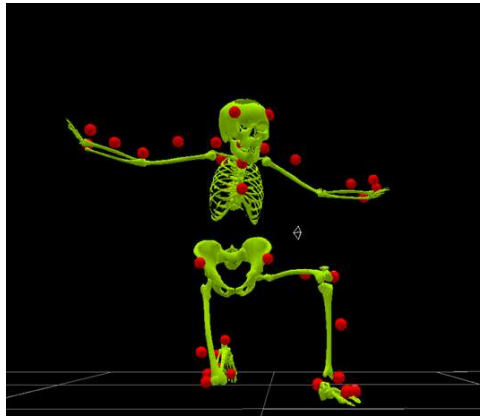
W. Ilg, PhD
M. Synofzik, MD
D. Brötz
S. Burkard
M.A. Giese, PhD
L. Schöls, MD

Neurology 2009; 73: 1823

Computerized movement analysis

- Recording of 3-dimensional movement trajectories by 41 reflecting markers using a VICON motion capture system
- Analysis of gait, stance, dynamic balance
  - Spatial and temporal variability
  - Variability in intra-limb coordination (hip and knee angles)
  - Center of gravity



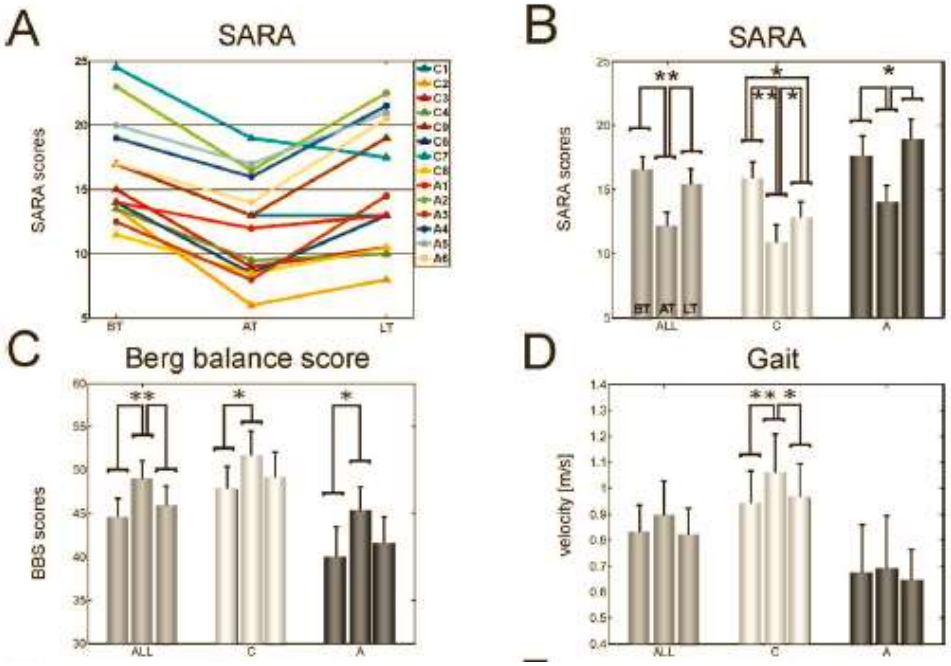


Long-term effects

Long-Term Effects of Coordinative Training in Degenerative Cerebellar Disease

Winfried Ilg, PhD,[1] Doris Brötz, PT,[2] Susanne Burkard, PT,[3] Martin A. Giese, PhD,[1] Ludger Schöls, MD,[4*] and Matthis Synofzik, MD[4]

Mov Dis 2010; 25: 2239



Long-term effects (1 year):

- Training effects persist in part after 1 year
- Effect size correlates with intensity of training at home
- Improvement includes every day functions
- Patients with cerebellar ataxia benefit more than afferent ataxias

Fall prevention

Gait & Posture 40 (2014) 247–251

Contents lists available at ScienceDirect

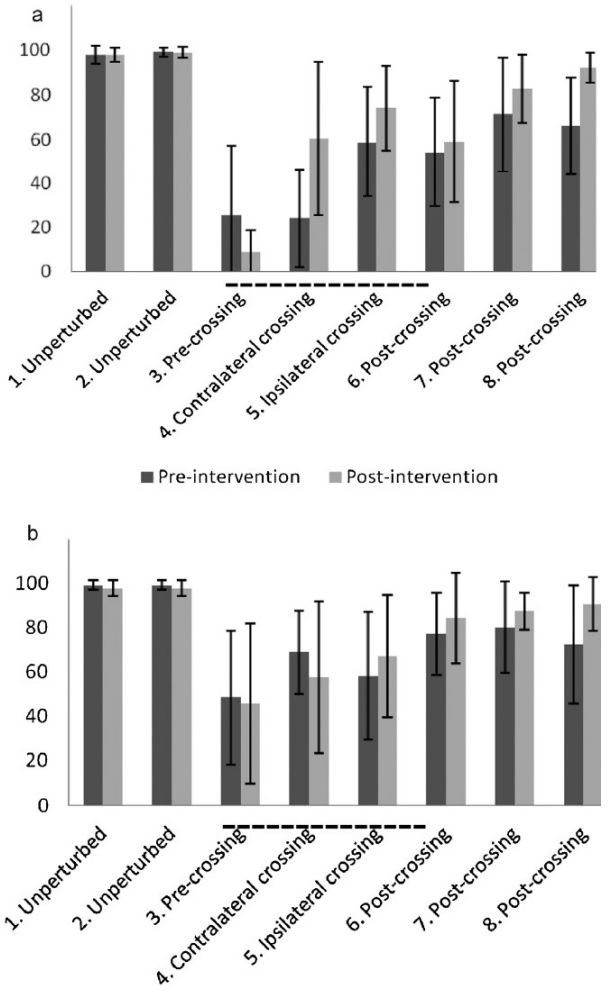
Gait & Posture

journal homepage: www.elsevier.com/locate/gaitpost

Gait adaptability training improves obstacle avoidance and dynamic stability in patients with cerebellar degeneration

Ella M.R. Fonteyn [a,b], Anita Heeren [c,d], Jasper-Jan C. Engels [c], Jasper J. Den Boer [c], Bart P.C. van de Warrenburg [a,*], Vivian Weerdesteyn [c,e]

- Gait adaptability training on obstacle avoidance and dynamic stability during adaptive gait
- 10 patients, 10x1h training in 5 weeks
  - Treadmill with visual stepping targets
  - Obstacles projected on the belt
- Improvement in
  - Obstacle task (EFAP)
  - SARA: 8.7±2.8 → 8.3±2.8
  - Falls: 0.8±1.0 → 0.4±0.7



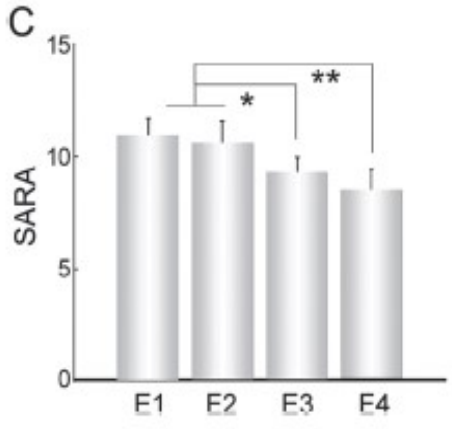
Evidence for video-based training

Author	Type of study	Disease	Age (year, mean ± SD)	Number of subjects	Intervention	Type of VR/VG	Protocol	Outcome measures	Main results	F
Ilg et al. [43] 2012	Prospective study	ADCA, FA, ARCA, AOA2	15.4 ± 3.5	10	Coordinative training based on commercial videogames	XBOX Kinect®	2 weeks lab training (4 1-h training sessions per week) – 6 weeks home training	SARA, DGI, ABC, motivation scale, gait parameters, goal-directed leg placement task	Improvements in coordination and balance	N
Santos et al. [44] 2017	Prospective study	SCA2, SCA3, SCA4, SCA10, ICA	41.6 ± 16.9	28	Virtual reality-based balance games	Nintendo® Wii	50 min per session, and 2 sessions per week for 10 weeks	DHI, BBS, SF-36	- Improvements in balance and gait, fall frequency, and patients' self-confidence - No adverse events reported	N
Schatton et al. [45] 2017	Prospective study	FA, AT, ARCA, AOA1	16.0 ± 7.4	10	Coordinative training based on commercial videogames	Nintendo Wii® and XBOX Kinect®	2 consecutive 6-week phases of exergaming training at home; 45 min per session, 3 times per week	SARA, GAS, quantitative movement analysis	Improvements in postural control and gait ataxia, individual goal attainment and sitting-body sway	N

He et al. J Neurol 2020

Video game-based training

Video game–based coordinative training improves ataxia in children with degenerative ataxia



- 10 „kids“ (11 – 20ys)
- 2 weeks lab-training + 6 weeks hometrainig with 3 Xbox video games for whole body coordination and dynamic balance

“Table Tennis”

upper extremity

“Light Race”

lower extremity

“20000 Leaks”

upper & lower extremity

- Improvement in SARA (2 pts) + digital movement recordings
- Benefit correlated with training intensity
- Advantages:
  - Cheap
  - At home
  - Fun - High motivation
  - Self-empowerment

Video games in advanced ataxia

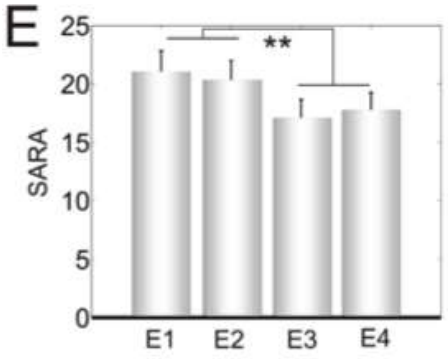

Parkinsonism and Related Disorders 39 (2017) 80–84

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

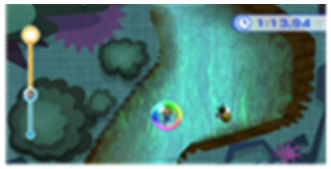
journal homepage: www.elsevier.com/locate/parkreldis

- 10 „kids“ (6 – 29ys; SARA 13 – 29 pts)
- 2x6 weeks of training with intermediate adaptation for improvement



- Improvement in SARA (2.5 pts)
- Effect size correlated with training intensity
- Benefit in goal attainment score

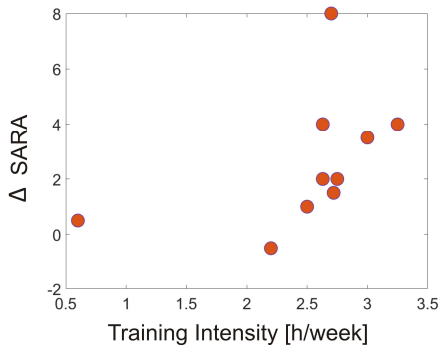
Penguin slide



Balance bubble

Table tilt

Ski slalom



Evidence for adapted physical acitivy training

Author	Type of study	Disease	Age (year, mean ± SD)	Number of subjects	Intervention	Protocol	Outcome measures	Main results
Song et al. [53] 2019	Case study	SCA2	39	1	Partnered tango dance therapy	1 h per session, and 3 times per week for 8 weeks	ICARS, SARA, BBS, FES, BI, gait parameters, the Beck Depression Index, the health-related QOL	Improvements in standing balance, gait, functional mobility, self-reported depression and QOL
Winser et al. [55] 2018	Prospective study	SCA3, SCA6, postinfectious cerebellar degeneration	50.9 ± 6.6	10	Yang style 8-form tai chi	1 h per session, and 3 sessions per week for 12 weeks	BBS, SARAbal, SARA, sensory ratio of somatosensory, SOT, LOS, BI	Improvements in balance and ataxia symptoms

He et al. J Neurol 2020

Speech therapy in ataxia

Journal of Neurology (2019) 266:1260–1266
https://doi.org/10.1007/s00415-019-09258-4

ORIGINAL COMMUNICATION

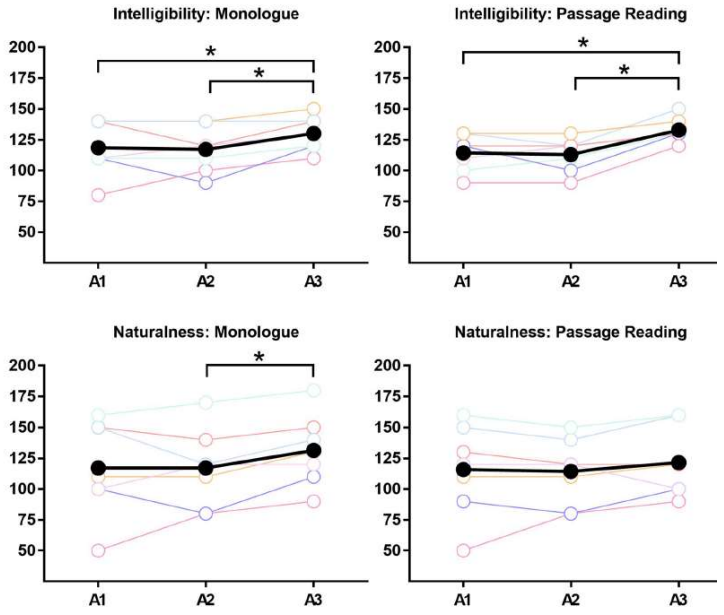
Speech treatment improves dysarthria in multisystemic ataxia: a rater-blinded, controlled pilot-study in ARSACS

Adam P. Vogel[1,2,3] · Lisa H. Stoll[1,4] · Andreas Oettinger[5] · Natalie Rommel[1,4] · Eva-Maria Kraus[1] · Dagmar Timmann[6] · Dion Scott[7] · Christina Atay[7] · Elsdon Storey[8] · Ludger Schöls[1,9] · Matthis Synofzik[1,9]

- 7 ARSACS patients (26–58ys; SARA 17–33 pts)
- 4 week program delayed listening feedback + realtime visual feedback + performance feedback

Improvement in:

- Rater blinded assessment of intelligibility
- Naturalness of speech
- Acoustic measures of speech



Intensity of physical therapy

- What training regime do you recommend to a mild to moderate affected patient (SARA: 10 points)?
    - Physical therapy once per week
    - Physical therapy three times per week
    - Home training: 20 minutes/day, 4 days/week
    - Home training: 2 hours/day, 7 days/week
    - Occupational therapy
    - Adapted physical activities

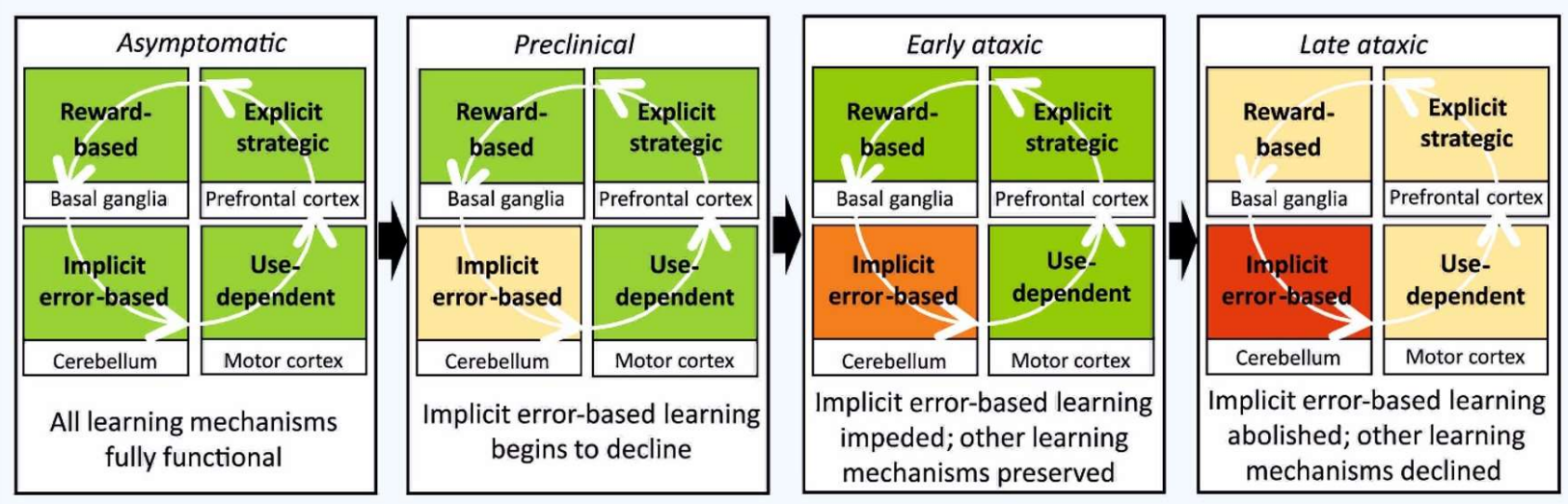
Summary

- Physiotherapy is able to improve balance and coordination as well as daily activities also in degenerative ataxias
- Long-term studies demonstrate long lasting effects
- Studies support training protocols with active exercises
- Training by whole-body controlled video games (exergames) is an enjoyable alternative to classical physiotherapy
- Beneficial effects seem to depend on
  - Intensity of exercise
  - Continuous training is required to preserve benefits

"Table Tennis"

Open questions

- When to start with physiotherapy?
  - Does training in presymptomatic stages of disease delay onset or progression?
- What is the optimal rehab concept?
  - Frequency and duration of training sessions?
  - Predictors of training success?
- Same training program in all stages of disease ?
  - Which compensatory motor learning strategies are preserved in early and late stages?
- Where does motor learning in cerebellar ataxias take place?
  - What is the morphological equivalent of motor learning in ataxias?



Donchin & Timmann Brain 2019

Key Points /Conclusions

- Rehabilitative training is effective in cerebellar ataxias
- Success requires individually tailored rehabilitation program
  - Different training for ambulant and wheelchair bound patients
  - Consider individual preferences to make training enjoyable
- Effect size correlates with training intensity
  - strongly depends on continuous training

Co-financed by the Connecting Europe Facility of the European Union

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‘
10. November 2020

European Reference Network | Neurological Diseases (ERN-RND)

This webinar has been supported by ERN-RND , which is partly co-funded by the European Union within the framework of the Third Health Programme “ERN-2016 - Framework Partnership Agreement 2017-2021."

Joint [illegible]eries

Doris Brötz

Winfried Ilg

Matthis Synofzik

THANK YOU

Next Webinar:

, Development of Sara-home: a novel assessment tool for patients with ataxia‘

by Gessica Vasco, Susanna Summa

24. November 2020, 15-16h CET