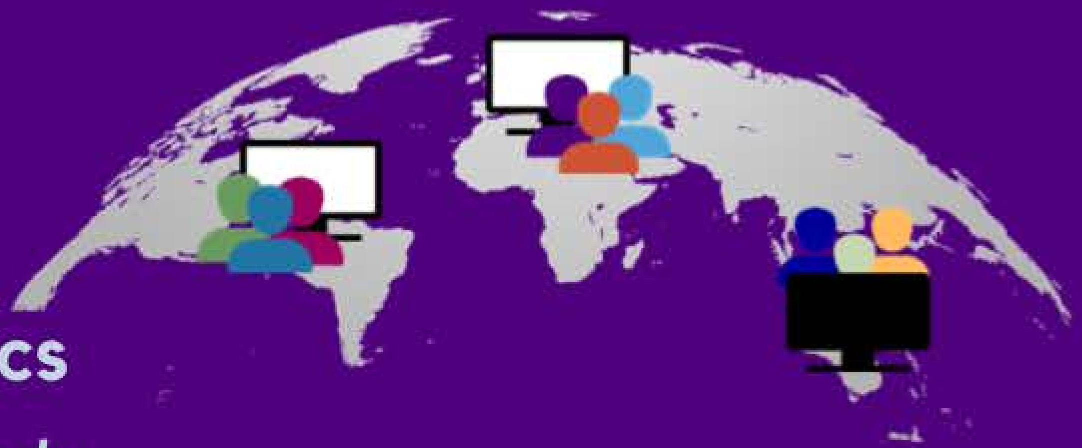
Ataxia Global Initiative
2nd Webinar Series:



iScience: AGI YII Webinar Series on Hot Topics

Explore Your Future in Ataxia Research

Quantitative Gait and Balance Outcomes for Ataxia Trials

Speakers: Fay Horak (Oregon Health and Science University, USA); Winfried Ilg (University of Tuebingen, Germany)

organized by the Young Investigator Initiative of the AGI

ATAXIA GLOBAL INITIATIVE
worldwide platform for clinical research in ataxias

Webinar 4:
Quantitative Gait and Balance Outcomes for Ataxia Trials

Fay Horak (Oregon Health and Science University, USA)

Winfried Ilg (Hertie Institute for Clinical Brain Research, University of Tübingen, Germany)

Digital-motor biomarkers - WP1 Balance & Gait

ATAXIA GLOBAL INITIATIVE
worldwide platform for clinical research in ataxias

Aim:

Standardize tasks, protocols, and measures of gait & balance as digital outcomes for multi-centre treatment assessments

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What restrictions do ataxia patients experience in every day life

Word cloud image of ataxia patients' answers to the question,

"What is most difficult for you in your everyday life? What restrictions do you experience?"

48 patients responded to these questions. Letter size corresponds with the number of patients who mentioned this topic.

[Gorcenco 2022, Cerebellum]

Goals on the way to a gait&balance endpoint

Standardize protocols and measures of gait & balance as digital outcomes for multi-centre treatment assessments

Review critical steps and clinimetrics needed for regulatory approval

a. Sensitivity/specificity of measures to mild-moderate ataxia

b. Correlated with the SARA and functional stagings, e.g. the FARS-ADL)

c. Sensitivity to change: longitudinal and interventions

d. Test-retest reliability, *Minimal Detectable Change* and

Minimal Clinically important Difference

e. Meaningfulness to patients

Recommended Recording Technology I

For suitability in multicenter clinical trials it is important to consider aspects:

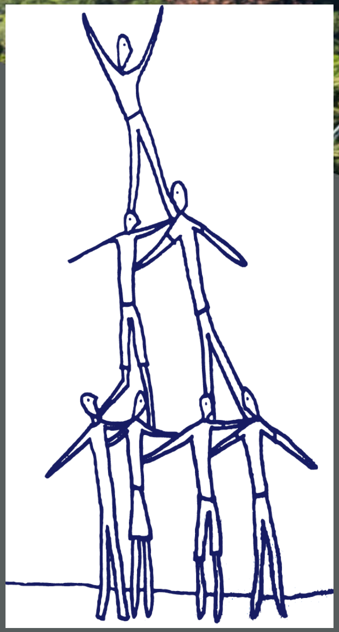
- cost
- feasibility without a dedicated gait laboratory or specialist staff,
- time required to prepare for the measurements,
- need of expertise in data processing,
- limitations in the spatial measurement range
- potential to characterize gait in daily life.

While laboratory-based, optical motion analysis systems remain the gold standard for gait analysis, they are expensive, resource intensive, and largely immobile, which limits their accessibility in clinical settings

- Wearable IMU sensor technology for quantifying gait and balance has recently become feasible for large, multicenter clinical trials without sophisticated gait laboratories or expert researchers.

Balance and Gait Digital Outcomes for Clinical Trials in Ataxia

Fay B. Horak, PhD, FAPTA
Endowed Professor of Neurology, Balance Disorders Laboratory of OHSU
Chief Scientist of APDM Precision Motion– Clario



Gait and Balance (Mobility) Impairment

A critical determinant of health and Quality of Life

Sensitive and Specific for Ataxias

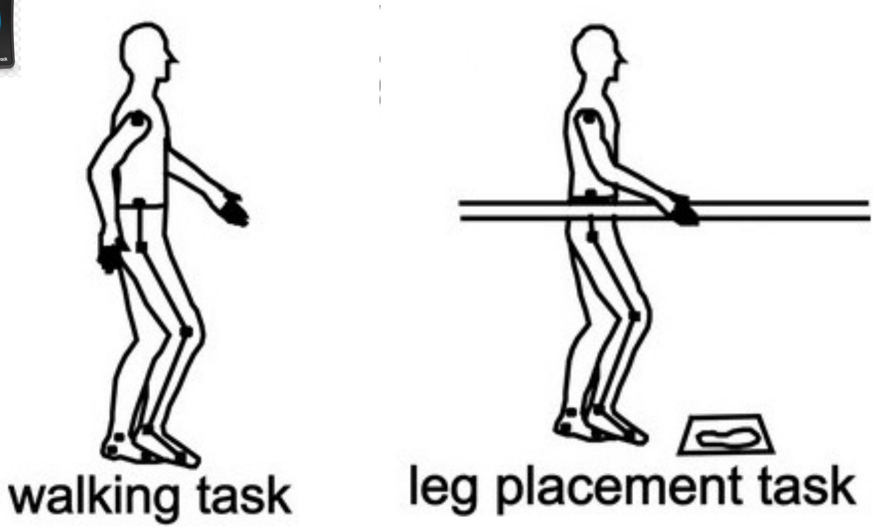
Questions:

- How can wearable technology provide digital balance and gait outcomes for clinical trials?
- Do gait impairments in ataxia reflect dyscoordination or imbalance?
- Which stance conditions are best to test standing balance?
- Are balance and gait characteristics similar in SCA subtypes (2,3,4, and 6) and Friedreich's Ataxia (FA)?
- Are digital balance and gait measures of ataxia related to disease severity and meaningful for patients?

Traditional Gold-Standard Methods to Quantify Gait and Balance in Ataxia show balance impairments.

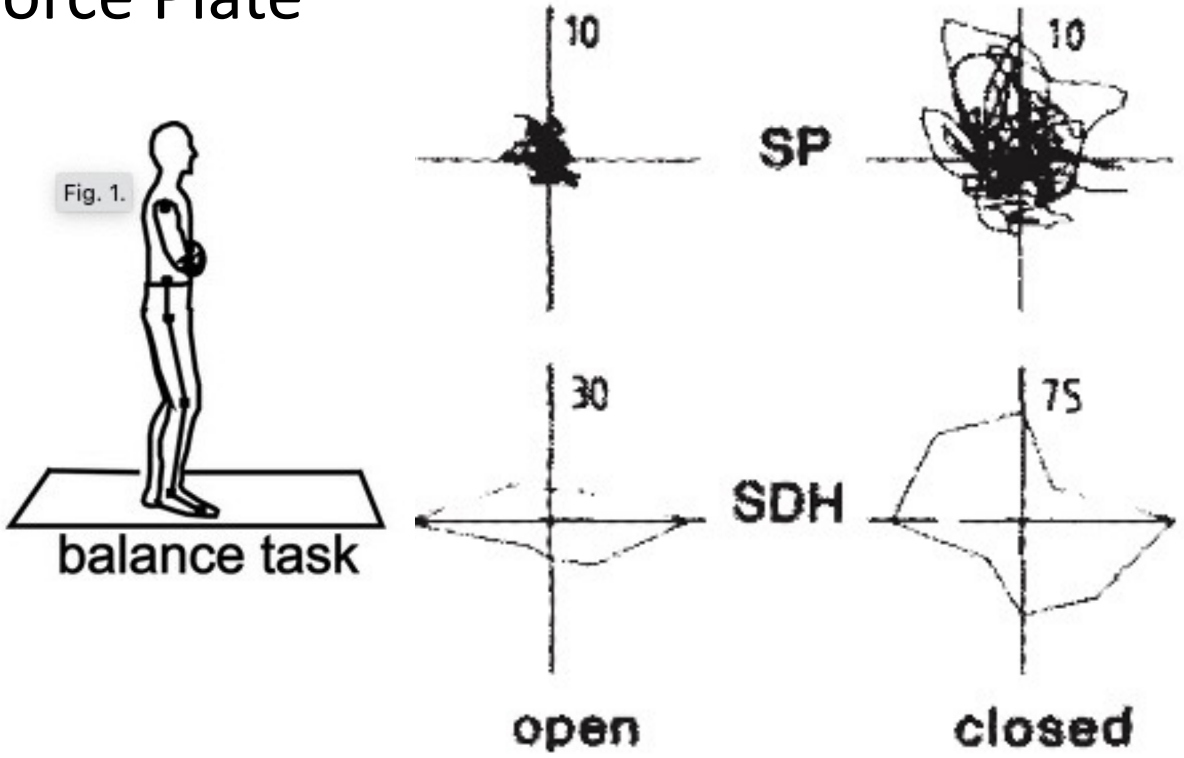
SCA is associated with variable gait characteristics and large postural sway.

Motion Capture for Gait



> "…balance deficits are more closely related to cerebellar gait ataxia than leg-placement deficits."

Force Plate



Postural sway with eyes open and closed in a patient with FA

Morton SM, Bastian AJ. Relative contributions of balance and voluntary leg-coordination deficits to cerebellar gait ataxia. Journal of neurophysiology 2003;89(4):1844-1856.

Diener HC, Dichgans J. Pathophysiology of cerebellar ataxia. Mov Disord 1992;7(2):95-109.

Disclosures

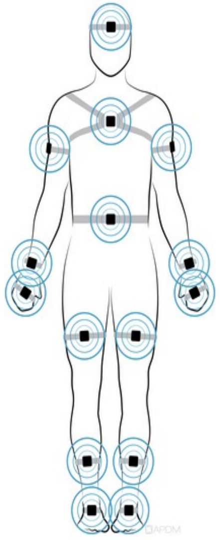
Dr. Horak is Chief Scientist of APDM Precision Motion, a Clario company that has a commercial interest in this research and technology. This conflict has been reviewed and managed by OHSU.

- Grants
  - ➢ Medtronic
  - ➢ Adamas
  - ➢ Abbott
  - ➢ Biogen
  - ➢ Pfizer
  - ➢ MJ Fox
  - ➢ NIH: NIA,
  - ➢ NIH: NCMRR,NINDS
  - ➢ DoD
  - ➢ MRF

- 30 seconds Stance
- 2 minute Walking (natural)

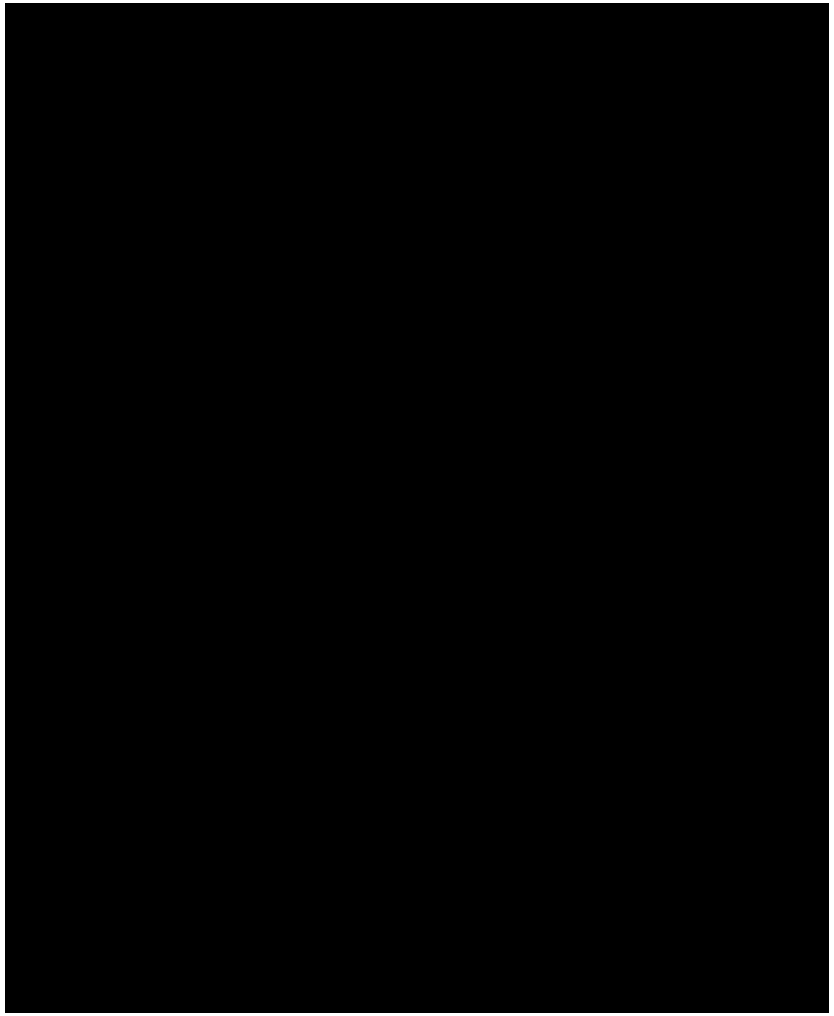
Opal IMU
by APDM

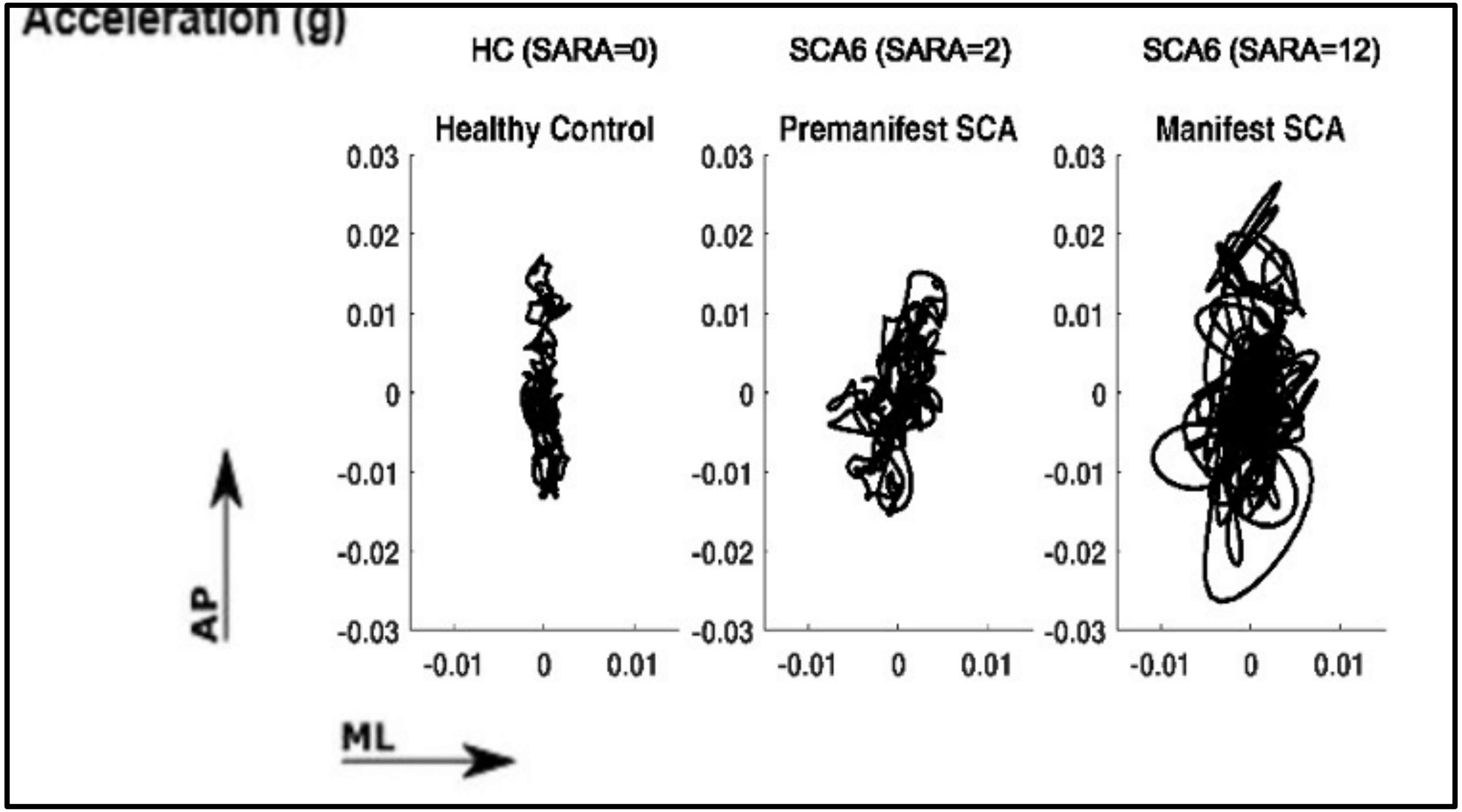
Instrumented 'Smart' Socks
by APDM



Mobility Lab
Software by APDM

Postural sway in standing is characteristic of SCA

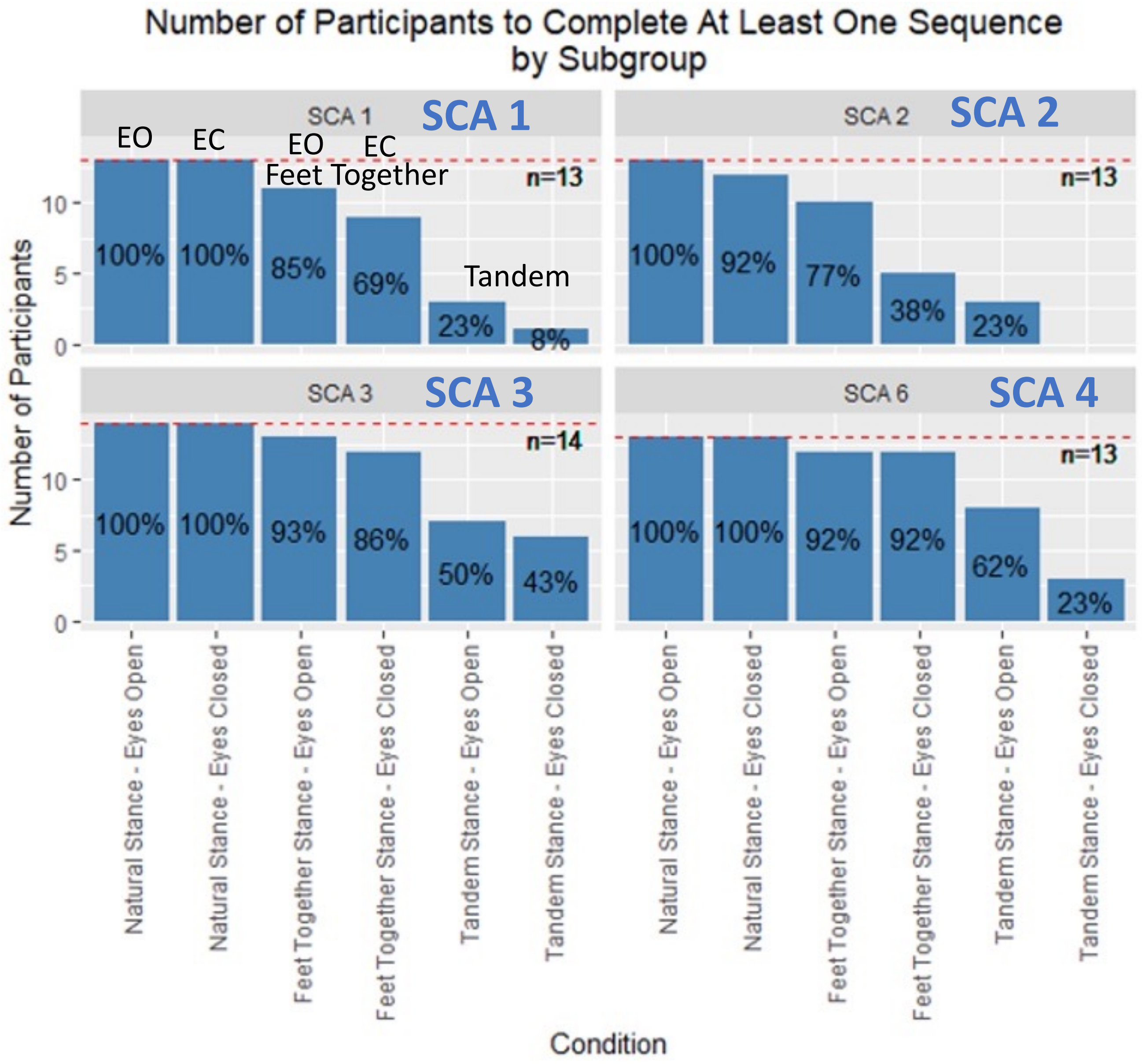


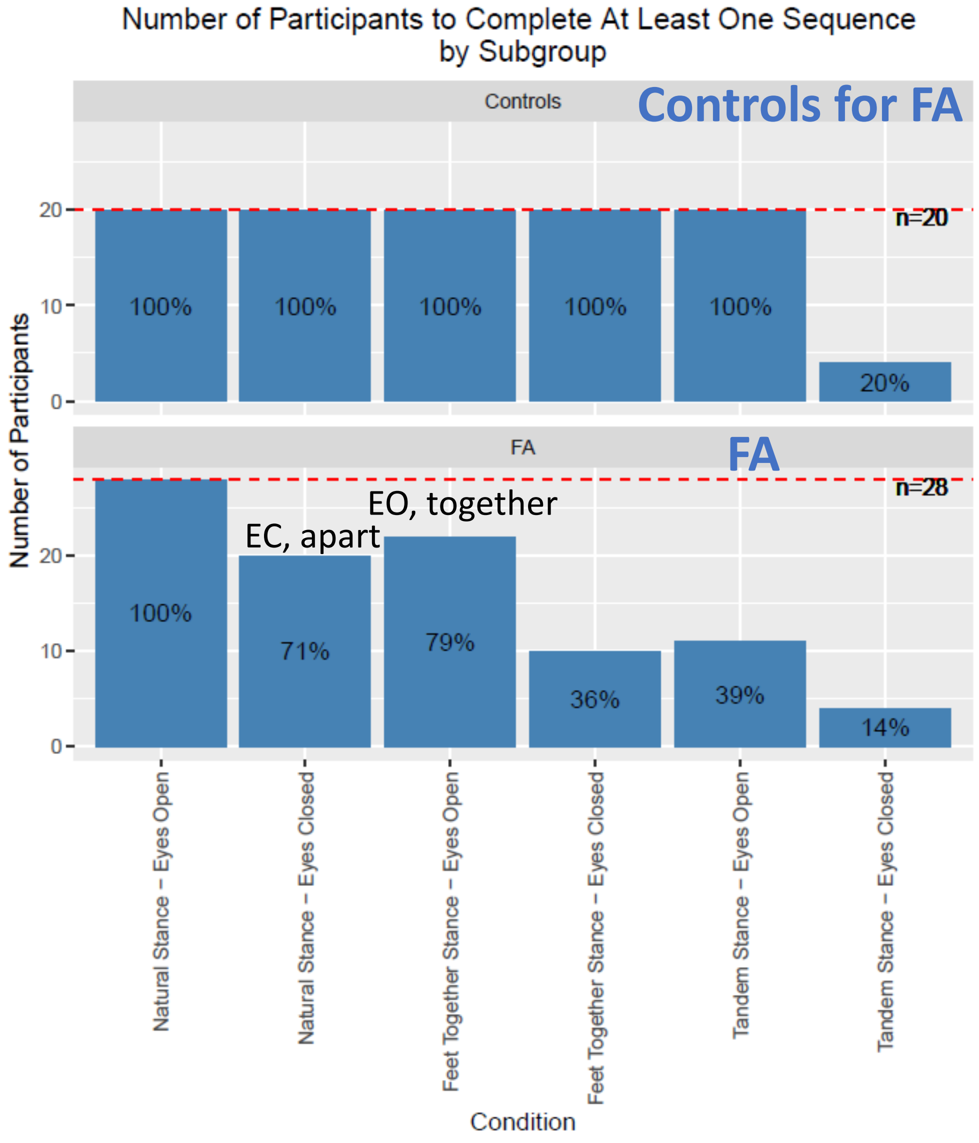


Postural sway during 30 sec standing EO, natural stance

SCA most successful (>80%) with EO and EC feet apart.
FA most successful (>80%) with EO feet apart and feet together.

186 SCA and 50 FA
50 Controls



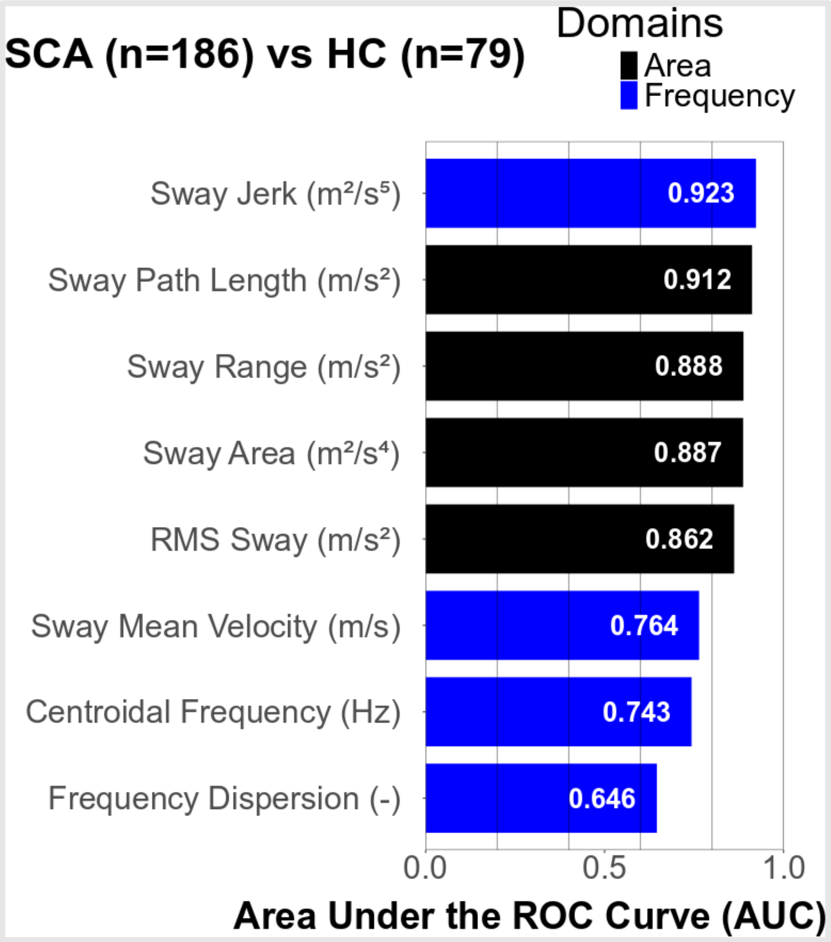


Measure	SCA ICC	SCA AUC	SCA P-value		FA ICC	FA AUC	FA P-value
Natural Stance – Eyes Open							
Sway Area	0.65	0.73	0.0009		0.87	0.95	<.0001
RMS Sway	0.59	0.73	0.005		0.83	0.96	<.0001
Natural Stance – Eyes Closed							
Sway Area	0.81	0.86	<.0001		0.94	0.99	<.0001
RMS Sway	0.81	0.85	<.0001		0.93	0.98	<.0001
Feet Together Stance – Eyes Open							
Sway Area	0.74	0.85	<.0001		0.88	0.99	<.0001
RMS Sway	0.70	0.84	<.0001		0.90	0.99	<.0001

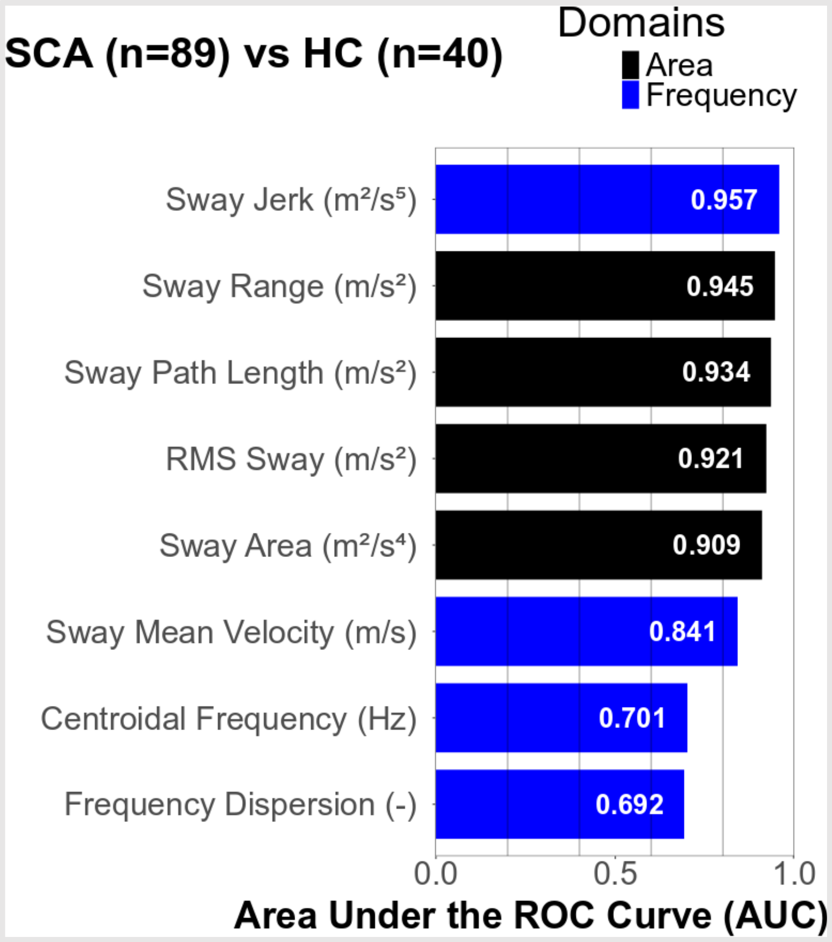
Reliability and Sensitivity are very good for the 3 least challenging stance conditions (although only 71% of FA could stand with feet apart EC),

SCA Discriminative balance measures (natural stance)

Eyes Open



Eyes Closed

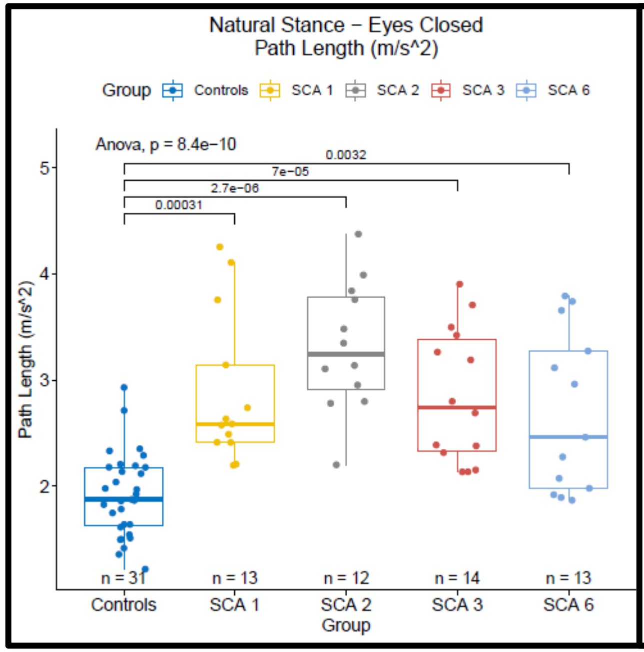


But, only 89/186 could stand with eyes closed

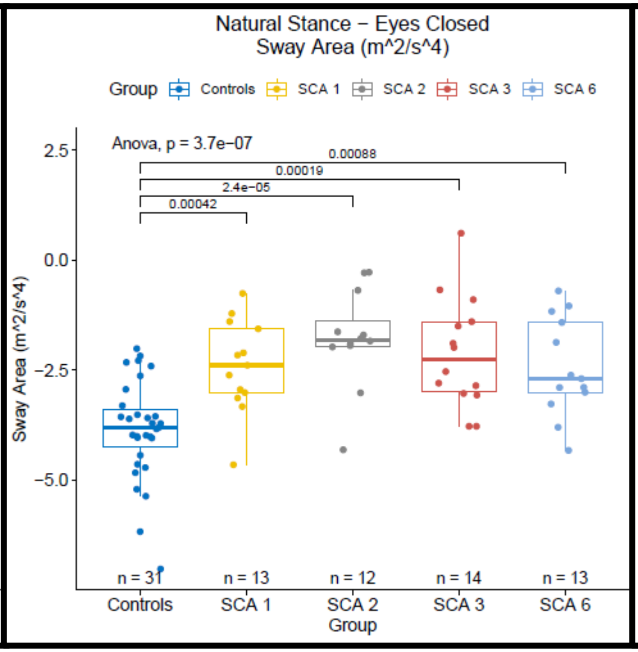
Shah Vrutangkumar V. et al. Presented at Ataxia Investigators Meetings 2022, in progress

Sway measures for SCA subtypes are significantly different from controls in natural stance condition

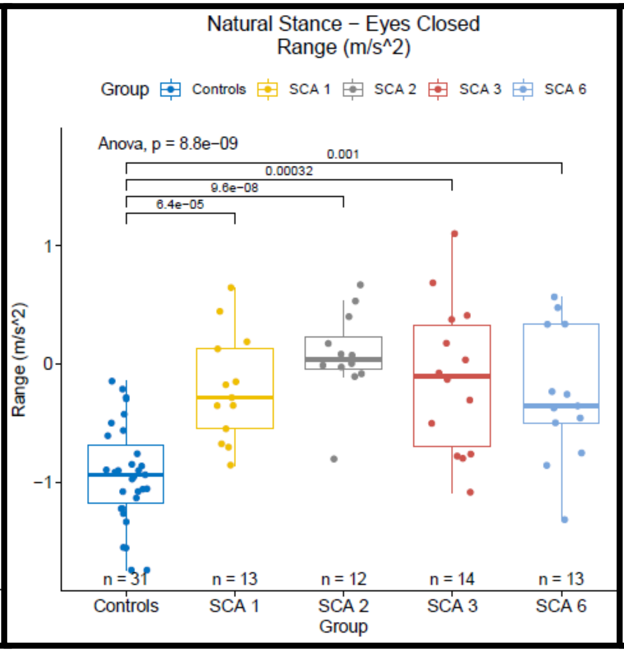
Sway Path



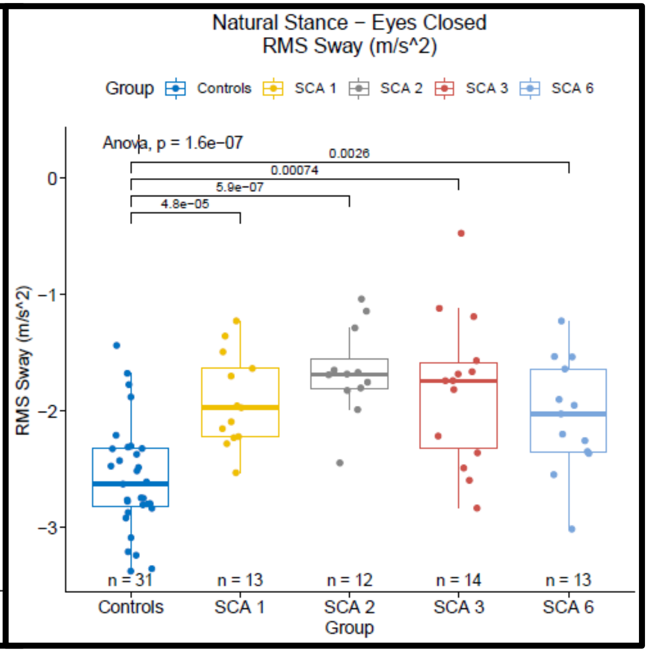
Sway Area



Range

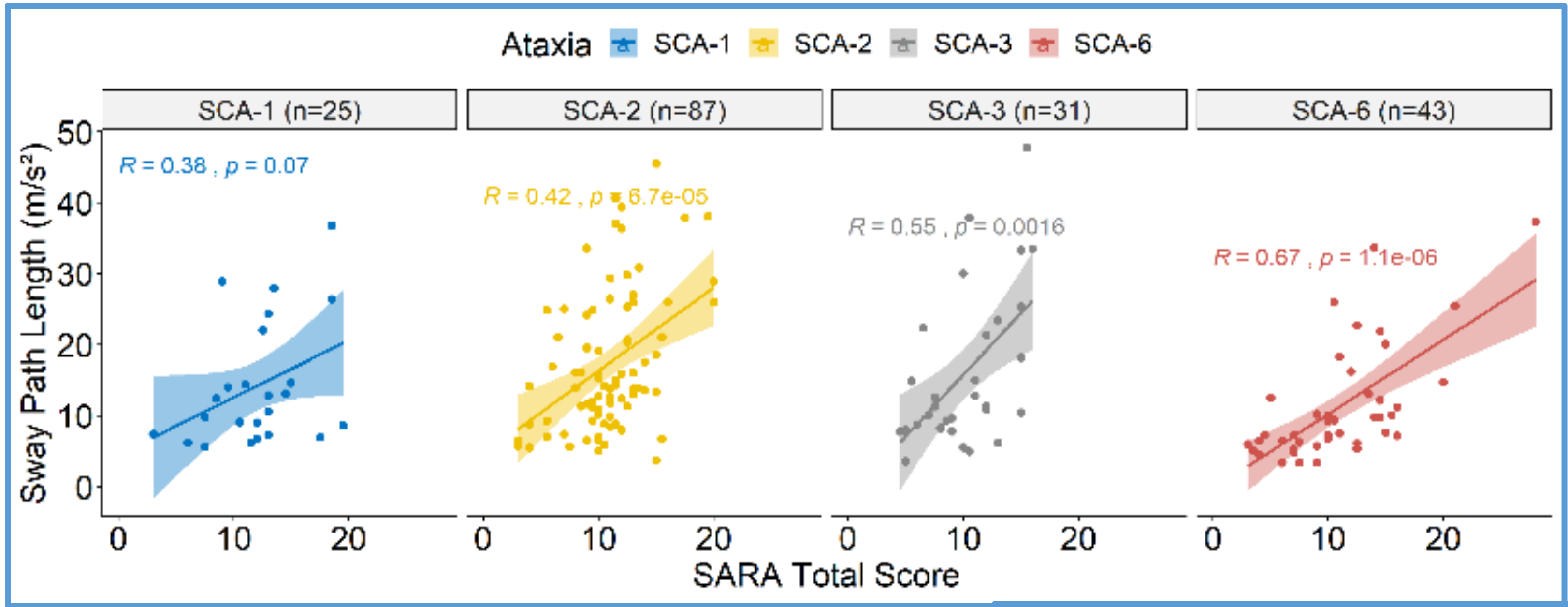


RMS

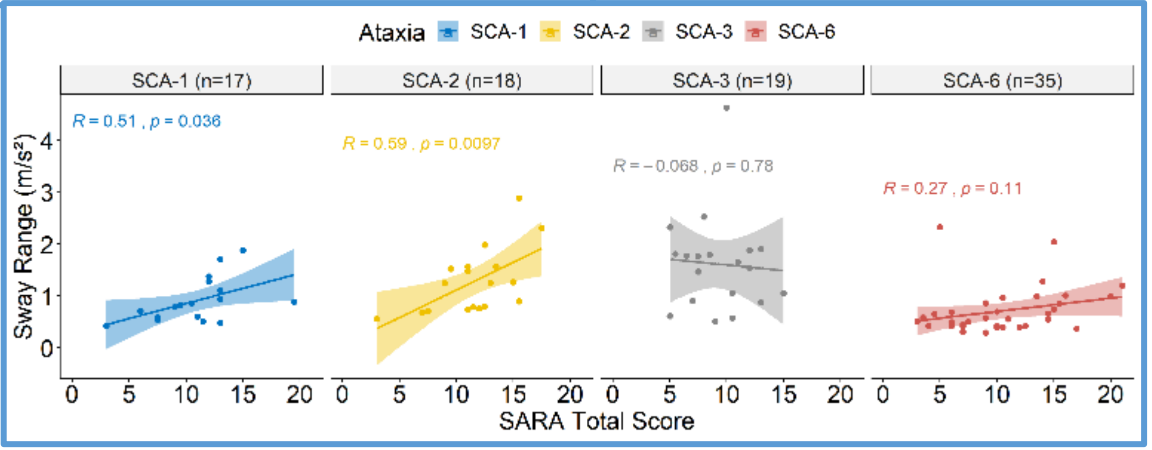


Shah Vrutangkumar V. et al. *Measures of postural sway can be used for Spinocerebellar Ataxia Clinical Trials* (In preparation)

Most discriminative balance measures correlate with SARA scores (particularly if eyes open)



Natural Stance
Eyes Open

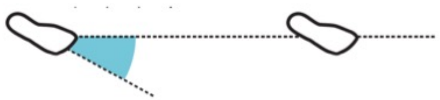


Natural Stance
Eyes Closed

Shah Vrutangkumar V. et al. Presented at Ataxia Investigators Meetings 2021

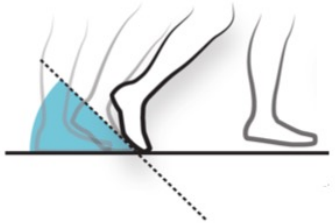
Ataxia subtypes show similar gait variability impairments reflecting impairments of dynamic balance

Toe Out Angle (degrees)

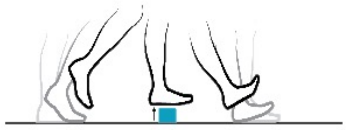


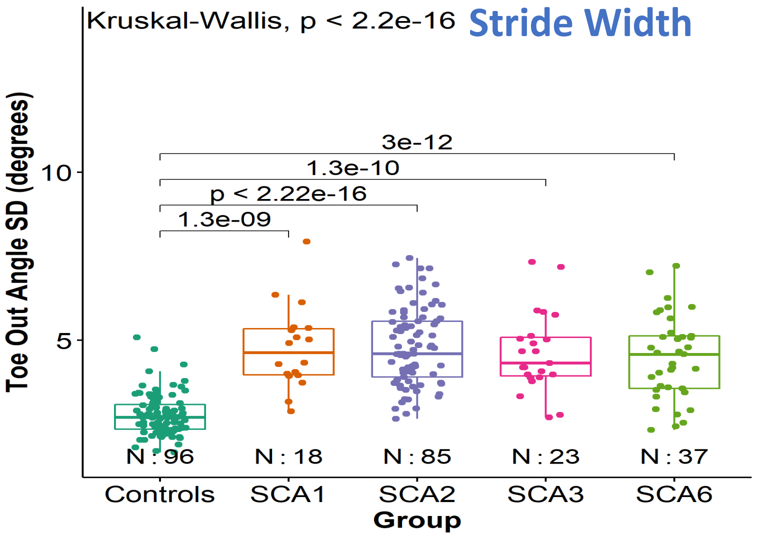
Double Support (%)

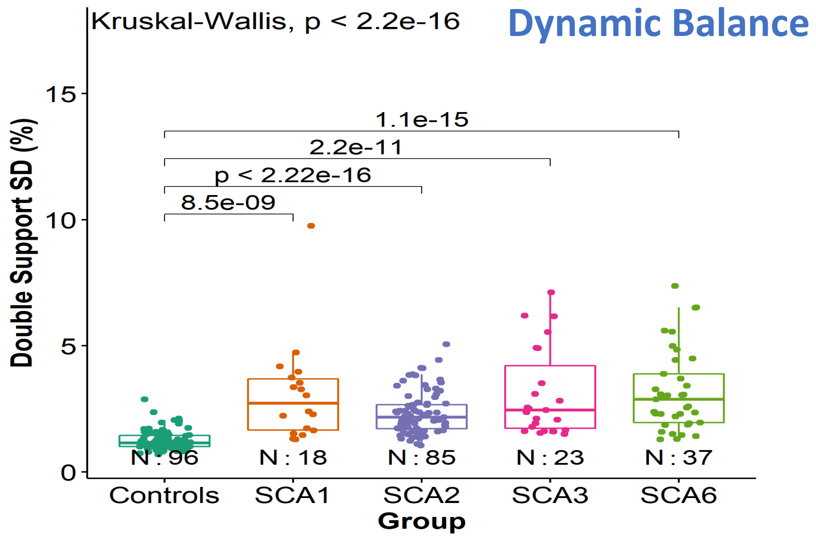
Toe Off Angle (degrees)

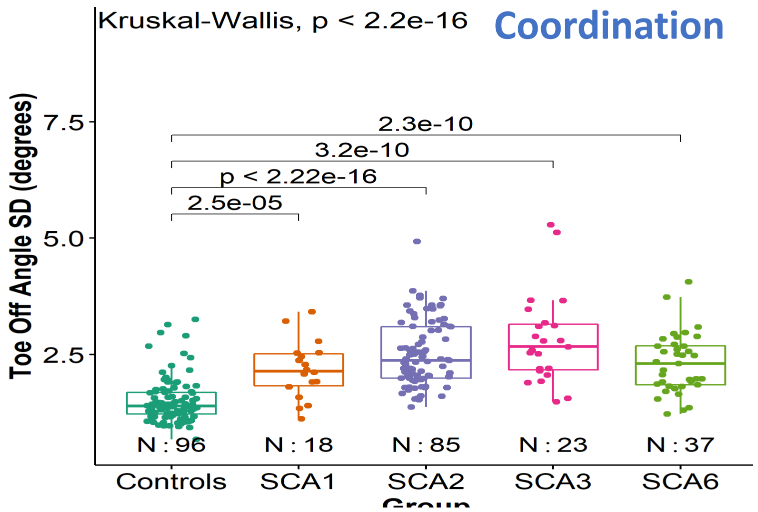


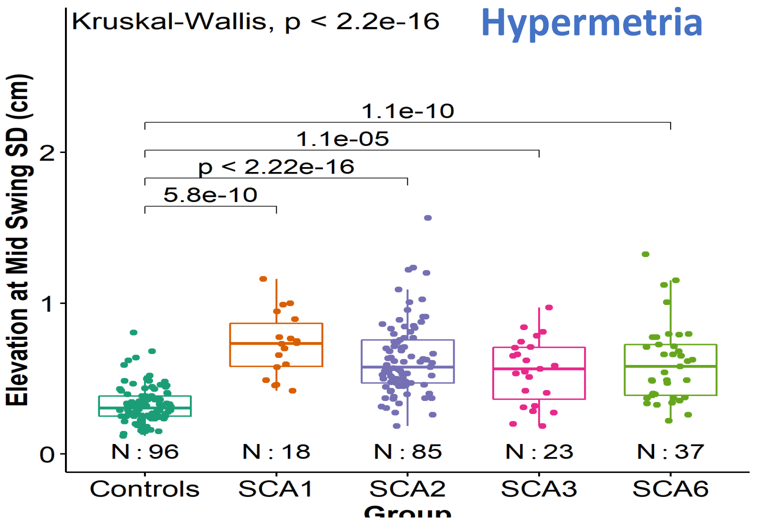
Elevation at Mid Swing (cm)



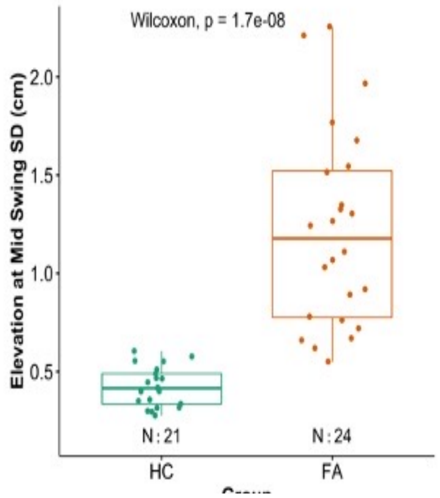








Friedreich's Ataxia Hypermetria



Shah et al. "Gait Variability in Spinocerebellar Ataxia Assessed Using Wearable Inertial Sensors." Movement Disorders 36.12 (2021): 2922-2931

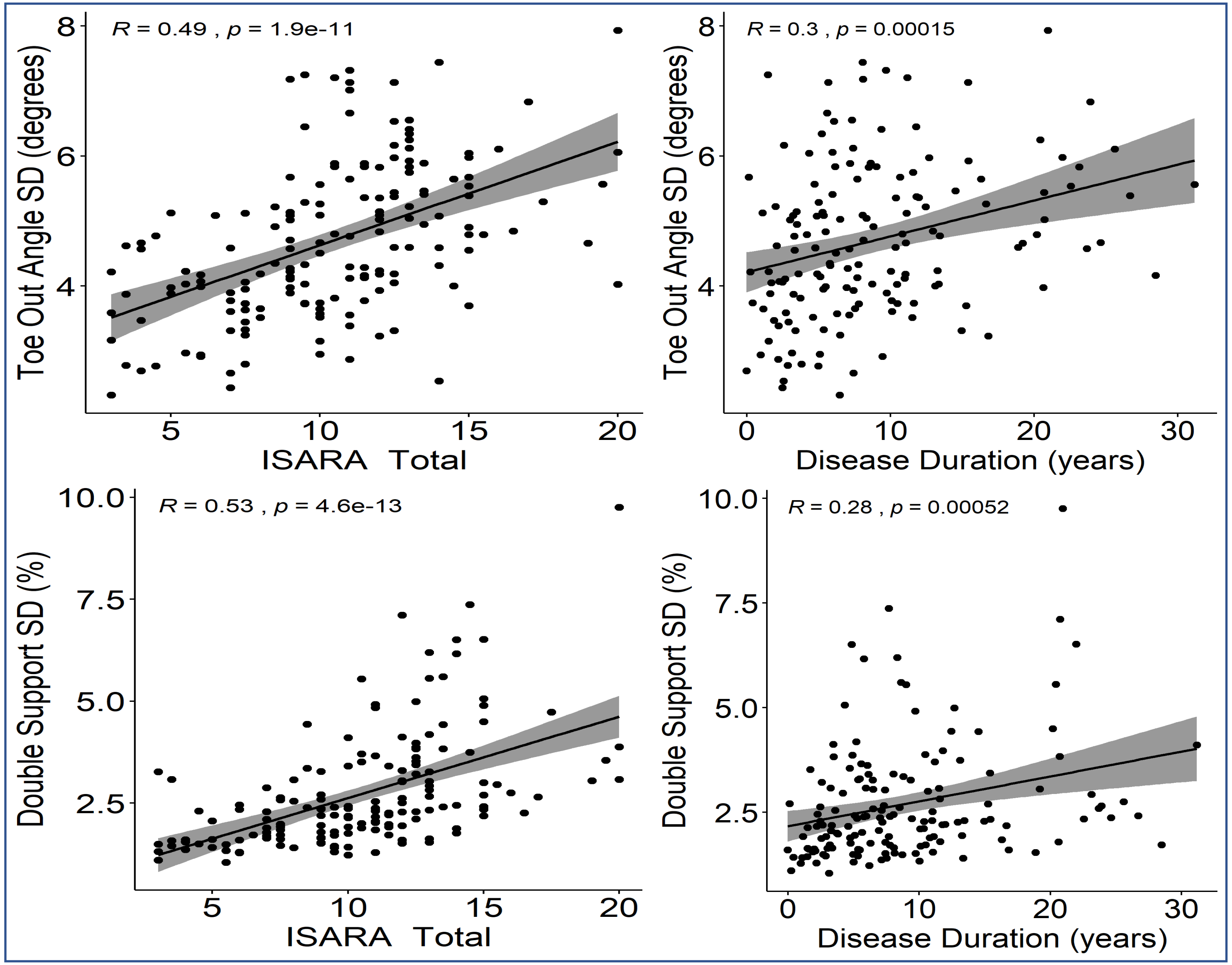
SCA and FA gait reliability + sensitivity was excellent

SCA Gait Metric	SCA ICC	SCA AUC	FA Gait Metric	FA ICC	FA AUC
Toe Off Angle SD (degrees)	0.94	.90	Trunk Transverse ROM SD (deg)	.89	.99
Elevation Mid Swing SD (cm)	0.90	.89	Elevation Mid Swing SD (cm)	.89	.99
Toe Out Angle SD (degrees)	0.85	.94	Toe Out Angle SD (degrees)	.83	.99
Double Support SD (%)	0.84	.93	Double Support SD (%)	.89	.99

SCA: Most discriminative gait measures were correlated with disease severity and duration

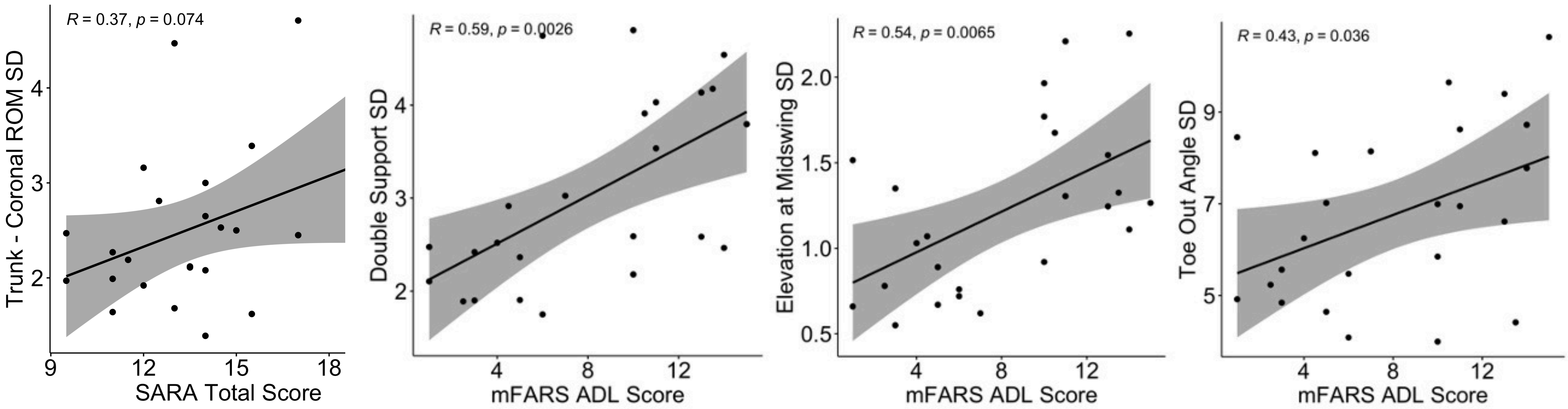
Toe Out Angle (Stride Width) Variability

Double Support variability



Shah Vrutangkumar V., et al. "Gait Variability in Spinocerebellar Ataxia Assessed Using Wearable Inertial Sensors." *Movement Disorders* 36.12 (2021): 2922-2931

FA: Most discriminative gait measures were correlated with disease severity (SARA) and mFARS ADL Score



Summary

- ✓ Wearable technology is feasible and practical for multisite clinical trials to quantify ataxic balance and gait.
- ✓ Standing balance and walking balance control deficits characterize SCA and FA severity.
- ✓ Standing balance conditions: SCA >80% EO and EC feet apart but FA >80% EO feet apart and EO feet together
- ✓ SCA gait is characterized by variability of foot placement whereas FA by variability of trunk rotation (and feet).
- ✓ Sensitive/specific digital outcomes are also reliable and correlated with disease severity and ADL scores (meaningful).

Sensitivity to longitudinal and interventional change

Upcoming clinical trials will aim to prove the therapy-induced slowing of progression within short time frames (1-2 years)

Degeneratice cerebellar Ataxia

Morton et al. 2010, Serrao et al. 2017, Shirai et al. 2019 , Ilg et al. 2022

→ Very heterogeneous in terms of populations, motion capture, duration, measures

Friedreich Ataxia

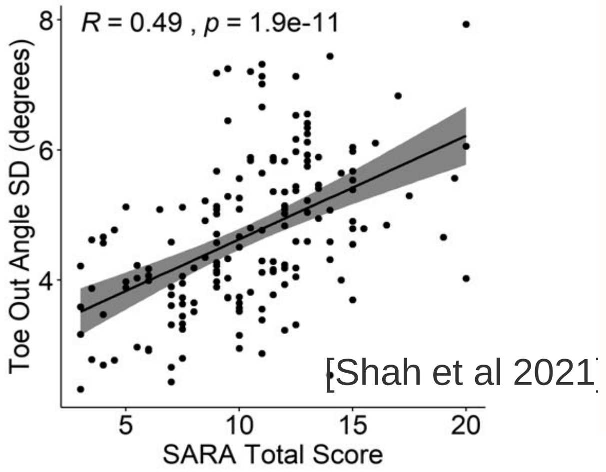
Milne et al. 2021
Summa et al. 2020
Zesiewicz et al. 2017
Vasco et al. 2016

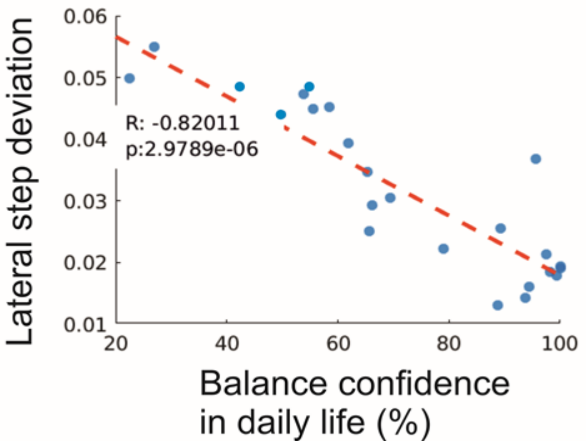
- Early onset, Adolescence and growth, typical neural maturation
- Faster progression to walking aid
- Gait speed as an effective measure
- Functional scores: BBS, dynamic gait index with higher effect sizes

.

Cross-sectional vs. longitudinal sensitivity

In various cross-sectional studies
gait variability measures (e.g. step length var)
revealed sensitivity to ataxia severity by
correlation to SARA, #Falls, ABC

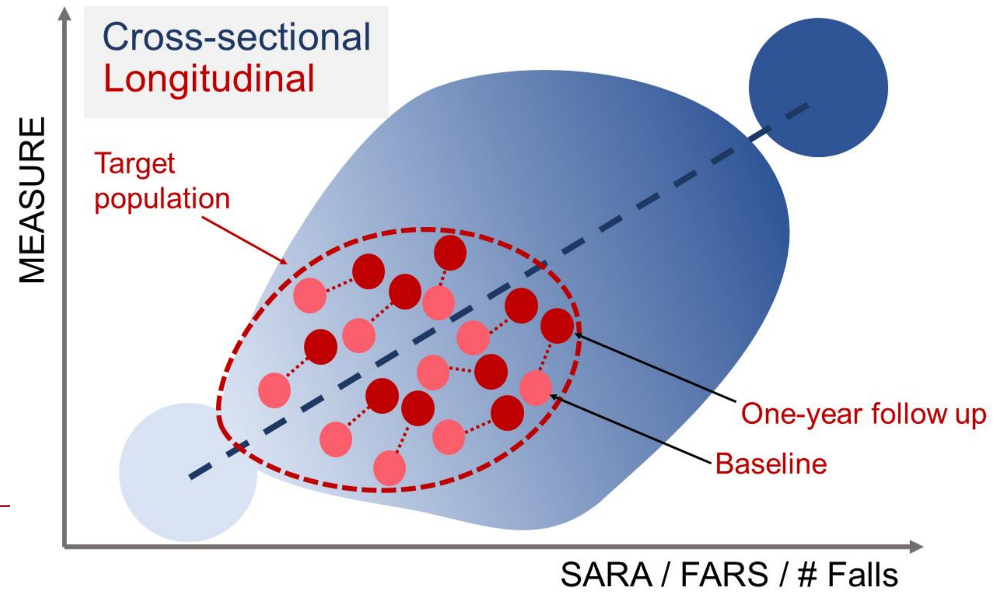




[Ilg et al 2022]

- However, these correlations can be strongly influenced by the range of disease severity.
- often predominantly driven by subjects at the ends of the spectrum

Sensitivity of motor biomarkers to ataxia severity

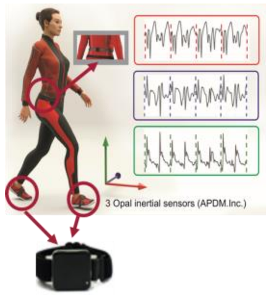


→ In trials, gait measures have to capture longitudinal change in short trial-like time frames (e.g. 1 year) with high effect size

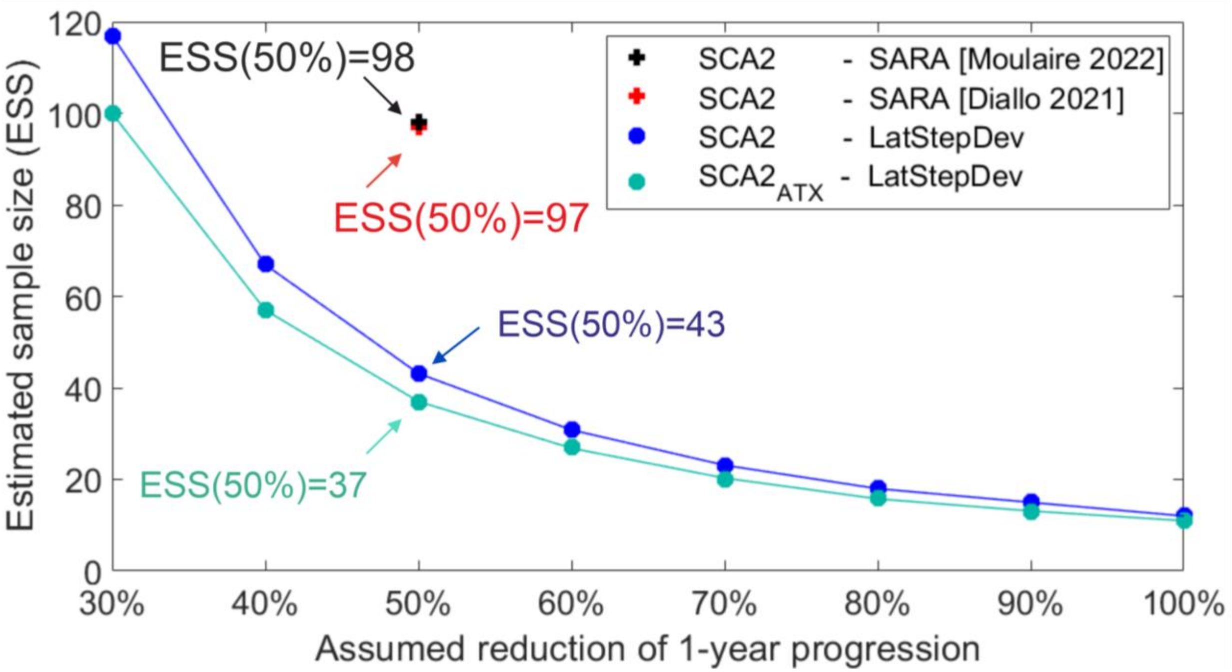
Sensitivity to change: longitudinal change in trial-like times frames

[Seemann et al 2023, in prep.]

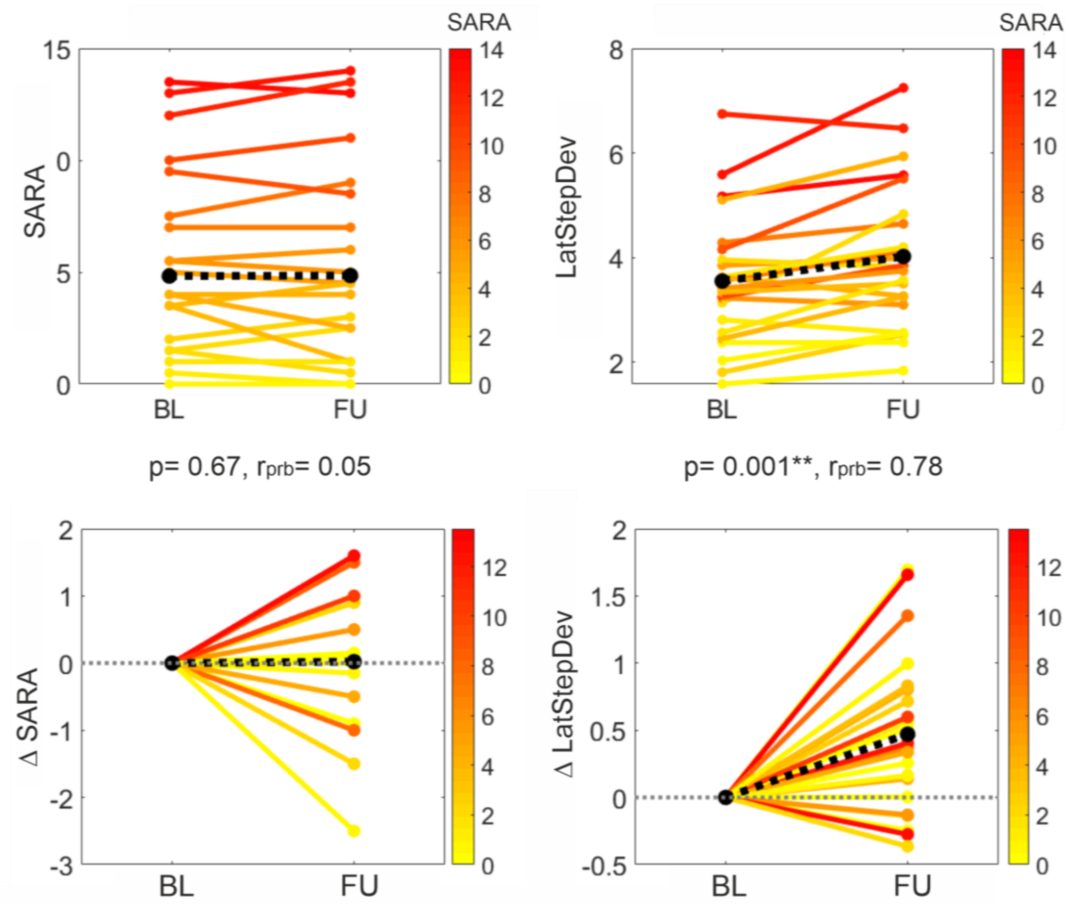
Multi-centre study, 2-min walk
(Paris- A. Durr, Tübingen)
SCA2 (#23, SARA mean 4.8)
including 8 pre-ataxic subjects



Sample size estimation for future intervention trials



SCA2 1-year progression of SARA and LatStepDev



→ Detection of longitudinal change in an early-stage SCA2 cohort, no SARA change

Test-Retest-Reliability and Minimal Detectable Change (MDC)

- Useful gait and balance outcomes need to demonstrate stability of measures over short time (intraclass correlation coefficients (ICCs), Bland-Altmann Plots
- Divide a 2 minute-walk test into two, 1-minute segments, and calculate the split-half reliability of gait measures ICC (Shah 2021)
- A more rigorous way to calculate test-retest reliability is to have the participants repeat the test twice, after a period of rest or on another day.
- MDC is critical in determining whether a treatment-related slowing of disease progression can be reliably detected or is lost in the measurement noise

$$MDC_{90} = 1.65 \times SD_{baseline} \times (\sqrt{2[1-ICC]})$$

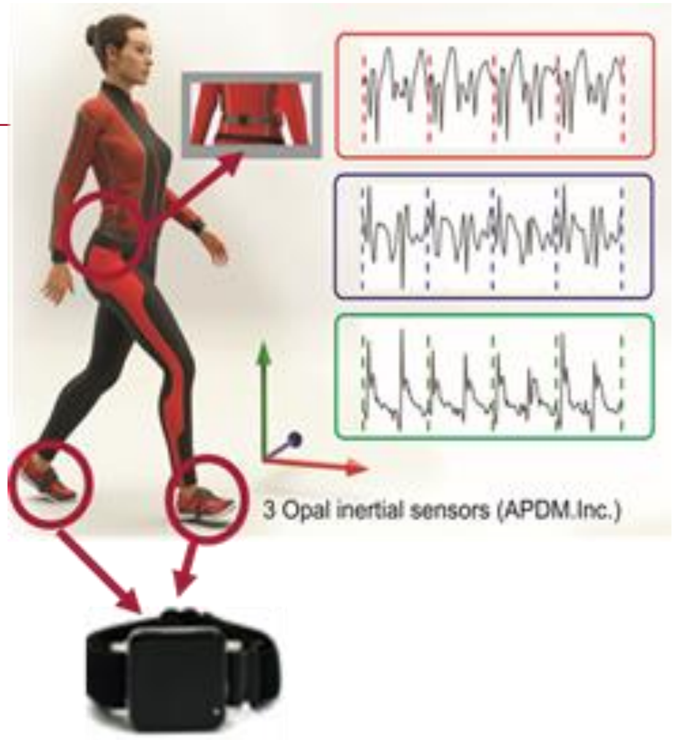
With 1.65 is the z-score of 90 % level of confidence

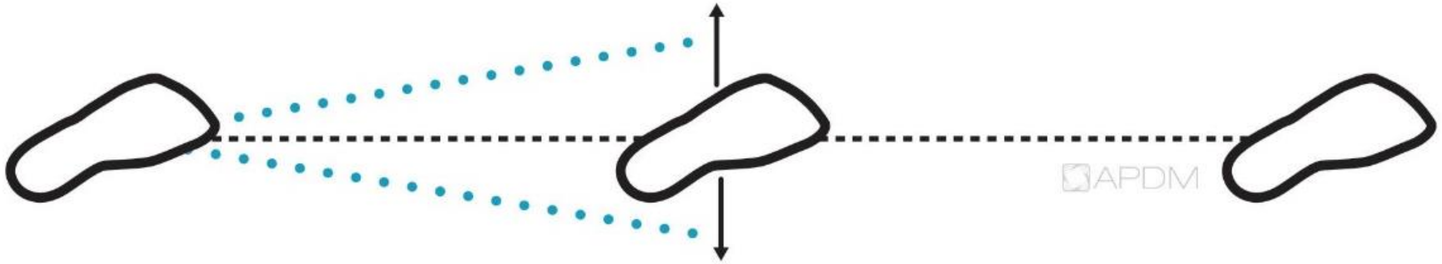
→ Longitudinal change to detect in the trial has to be larger than MDC

Gait measure: Lateral step deviation

- LatStepDev: calculating the absolute perpendicular deviation of the midfoot position from the line connecting the 1. and the 3. step

- LatStepDev is highly correlated with
  - SARA, SARA g&p
  - the patient-reported subjective balance confidence (ABC score) → meaningful to patients
  - both laboratory-based gait assessment and real-life recordings (more robust than stride length var in real life)





From lab-based gait assessment to real life walking

BENEFITS

- More data
- Behavior not Ability
- Ecologically valid
- More sensitive
- Fewer subject visits

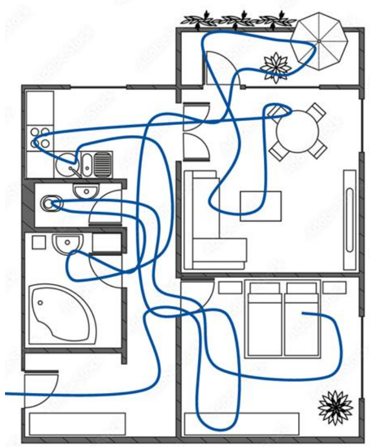
CHALLENGES

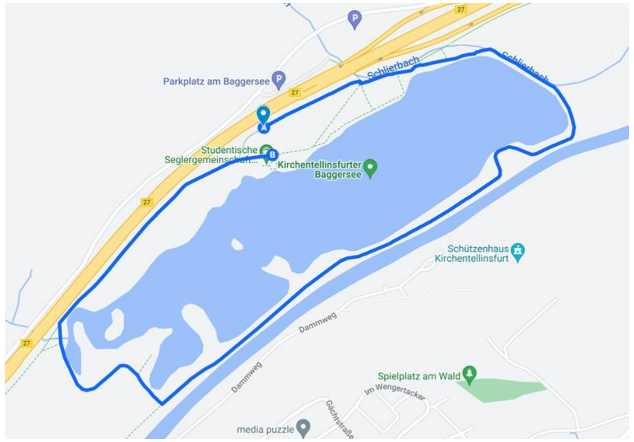
- Compliance
- Less controlled
- Higher Variability
- Context-dependent influence on gait

How can we compare longitudinal real life assessments ?

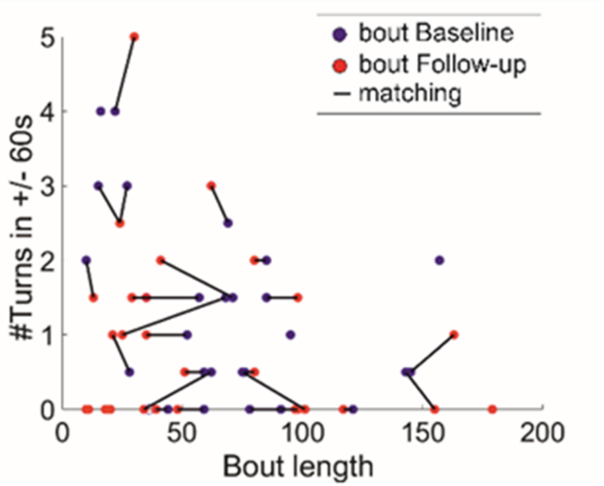
- We want to detect longitudinal changes in dynamic walking behavior after 1 year
- Comparison of gait variability parameters will be highly influenced by differences in amount and types of activities and walking behaviors

→ Need to select comparable walking bouts





- Context is estimated by macroscopic gait parameters
  - bout length
  - #turns in +/- 60s
- 1:1 matching of bouts from different assessments (follow-up) with similar macroscopic gait parameters



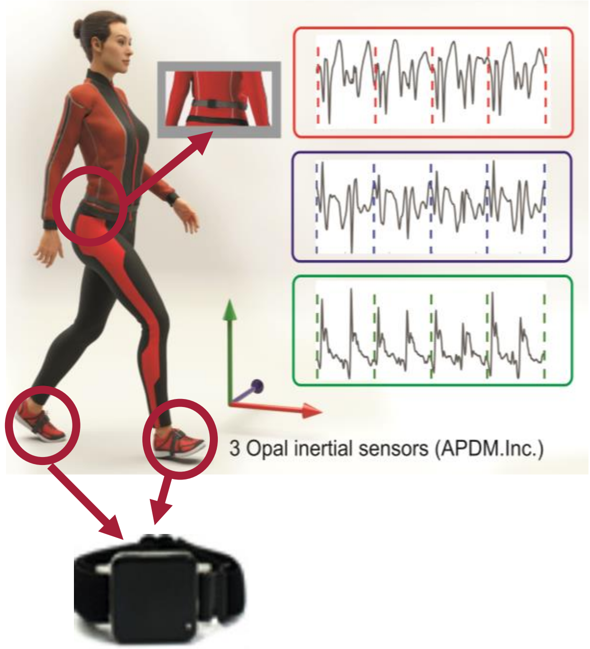
[Seeman et al, in preparation]

Longitudinal Study – lab assessment and real-life recordings

Baseline → 1.Year Follow-up → 2.Year Follow-up

- 24 patients with deg. cerebellar disease (SARA:9.4±3.9, [1:16]), 31 controls
  - 13 SCA1/2/3

- Measures:
  - Spatio-temporal step variability
  - Lateral step deviation
  - Compound measure spatial variability (combining Lateral step deviation & Step length variability)



[Seeman et al, in preparation]

Longitudinal Results

Condition	Measure	1-year FU	effect size	2-years FU	effect size
Clinics	SARA	0.164	0.313	**0.021***	0.714
	$SARA_{gp}$	0.097	0.463	**0.023***	0.736
Lab	StrideL	0.376	0.207	**0.02***	0.550
	LatDev	0.475	0.167	**0.007****	0.671
	SPCmp	0.253	0.267	**0.005****	0.697
	ROMcor	0.732	-0.080	0.741	0.082
Real Life	StrideL	0.063	0.433	**0.016***	**0.769**
	LatDev	**0.005****	**0.660**	**0.016***	**0.769**
	SPCmp	**0.004****	**0.680**	**0.009****	**0.821**
	ROMcor	**0.028***	**0.513**	**0.021***	**0.744**

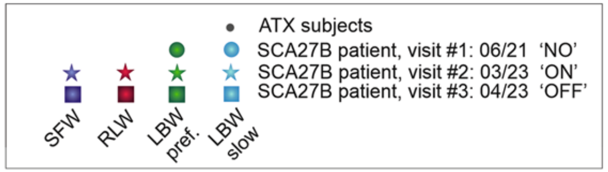
[Seeman et al, in preparation]

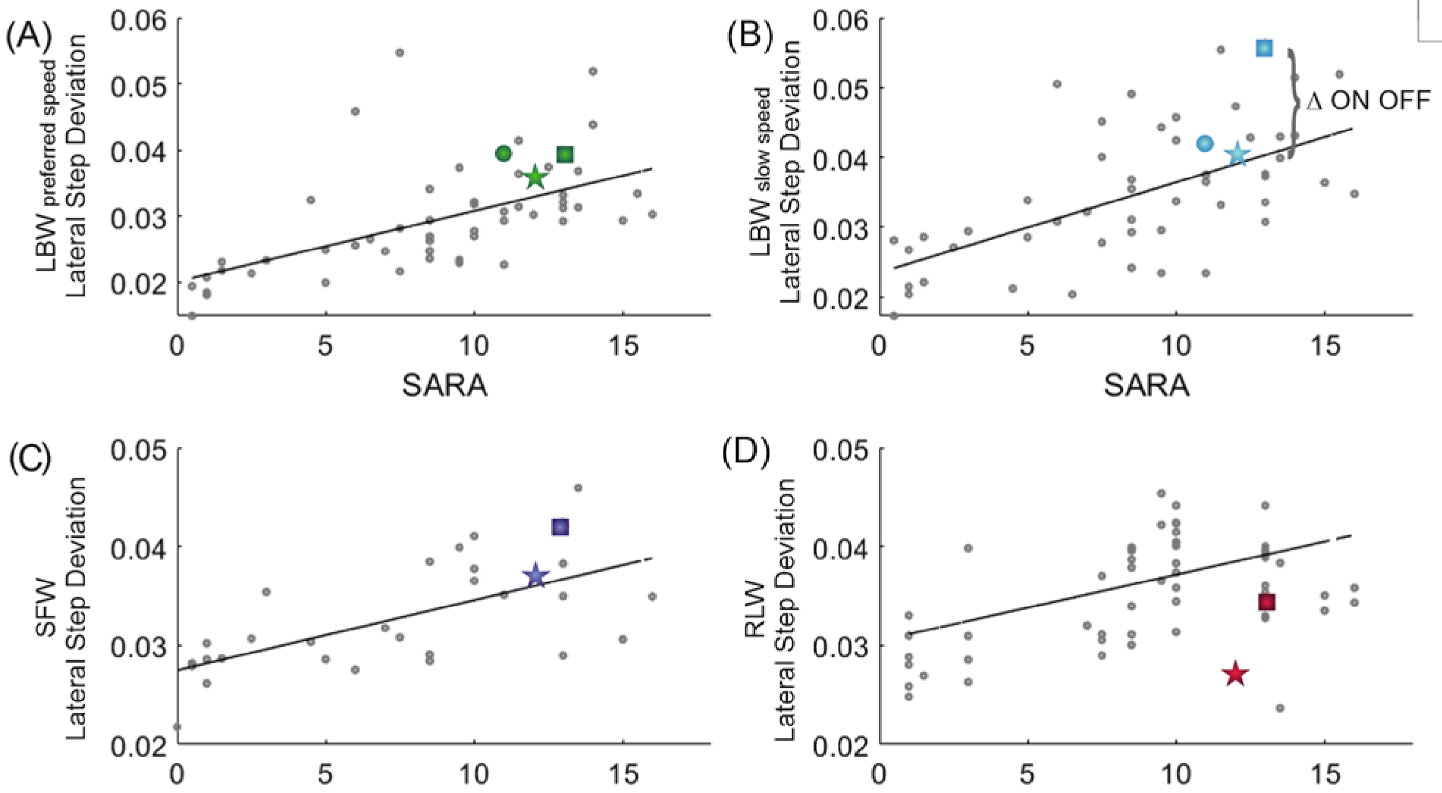
Treatment trial – symptomatic drug

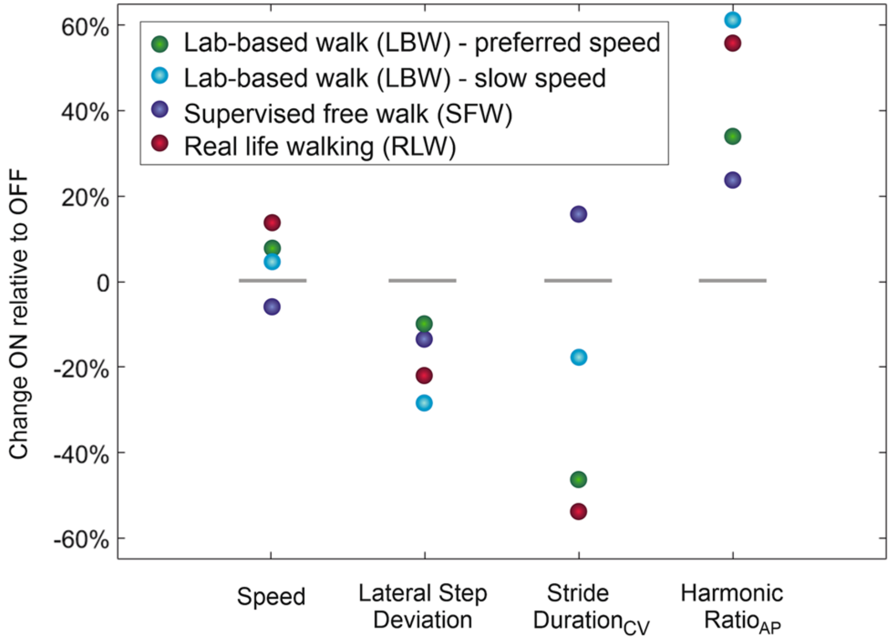
4-Aminopyridine improves real-life gait performance in SCA27B on a single-subject level: a prospective n-of-1 treatment experience

[Seemann, J. Neurology,2023]

Gait measure “Lateral Step Deviation” in different walking conditions







→ Change in LatStepDev associated with change in PGI, no SARA change

Summary

a) Sensitivity/Specificity: Identify gait and balance measures that robustly separate individuals with ataxia from age-matched controls; V

b) *Concurrent Validity:* Include standard neurological scales of severity (e.g. SARA); V

c) *Longitudinal assessment of natural course:* Demonstrate longitudinal changes over a reasonable study period ●●○ → few individual studies

d) *Test-retest reliability* and *Minimal Detectable Change* (MDC); ●●○

e) *Meaningfulness:* Calculate *Minimal Clinically Important Change* MCID for sensitive digital measures by including a patient-reported scale of perceived change; ●○○

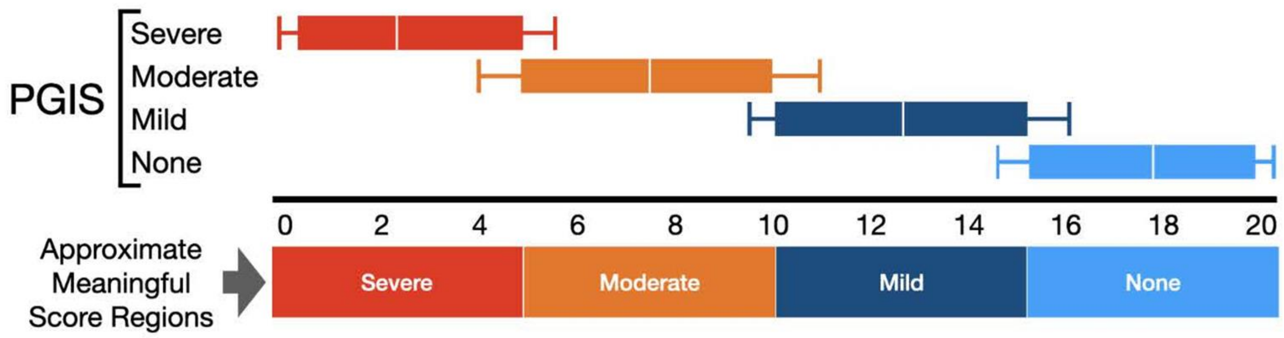
f) *Daily life:* monitoring of walking behavior ●◐○

→ Best outcome ●●○

What is missing - Next important steps

- Meaningfulness to patients
  - Associate changes in gait measures to patient-reported outcomes

Figure 1. Example of Approach for Interpreting COA Scores in Terms of Meaningful Score Regions Corresponding to Patient Global Impression of Severity (PGIS).



[FDA 2023]

- Different proposed measures in individual studies → Important to establish a common longitudinal gait database to harmonize the results of different algorithms and measures

- Establish a common protocol -> AGI consensus paper (still under review)
  a) *Protocol:* Include a 2-minute walk (10 meters) and a 30-second standing task with additional conditions or greater challenge for preataxic ataxia;

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Thank you for your attention !

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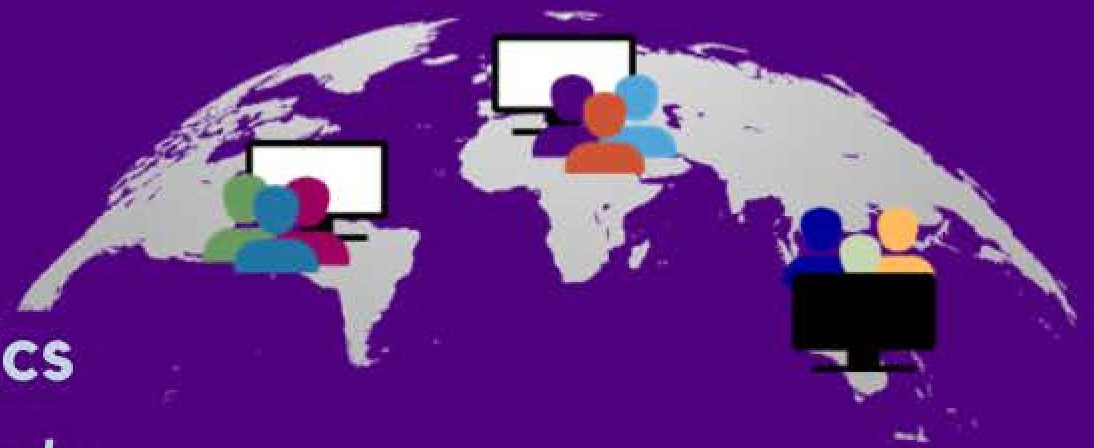

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