ARTICLE CLASS OF EVIDENCE

Real-life gait assessment in degenerative cerebellar ataxia

Toward ecologically valid biomarkers

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Abstract

Objectives

With disease-modifying drugs on the horizon for degenerative ataxias, ecologically valid motor biomarkers are highly warranted. In this observational study, we aimed to unravel and validate markers of ataxic gait in real life by using wearable sensors.

Methods

We assessed gait characteristics of 43 patients with degenerative cerebellar disease (Scale for the Assessment and Rating of Ataxia [SARA] 9.4 ± 3.9) compared with 35 controls by 3 body-worn inertial sensors in 3 conditions: (1) laboratory-based walking; (2) supervised free walking; (3) real-life walking during everyday living (subgroup n = 21). Movement analysis focused on measures of spatiotemporal step variability and movement smoothness.

Results

A set of gait variability measures was identified that allowed us to consistently identify ataxic gait changes in all 3 conditions. Lateral step deviation and a compound measure of spatial step variability categorized patients vs controls with a discrimination accuracy of 0.86 in real life. Both were highly correlated with clinical ataxia severity (effect size ρ = 0.76). These measures allowed detecting group differences even for patients who differed only 1 point in the clinical SARA$_{posture\&gait}$ subscore, with highest effect sizes for real-life walking (d = 0.67).

Conclusions

We identified measures of ataxic gait that allowed us not only to capture the gait variability inherent in ataxic gait in real life, but also to demonstrate high sensitivity to small differences in disease severity, with the highest effect sizes in real-life walking. They thus represent promising candidates for motor markers for natural history and treatment trials in ecologically valid contexts.

Classification of evidence

This study provides Class I evidence that a set of gait variability measures, even if accessed in real life, correlated with the clinical severity of ataxia in patients with degenerative cerebellar disease.

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Glossary

AP = anterior-posterior; **CA** = cerebellar ataxia; **CA_{Mild}** = mild cerebellar ataxia; **CA_{Mod}** = moderate cerebellar ataxia; **CA_{Sev}** = severe cerebellar ataxia; **CI** = confidence interval; **CV** = coefficient of variation; **DCA** = degenerative cerebellar ataxia; **HC** = healthy control; **INAS** = Inventory of Non-Ataxia Signs; **LatStepDev** = lateral step deviation; **LBW** = laboratory-based walking; **RLW** = real-life walking; **ROC** = receiver operating characteristic; **SARA** = Scale for the Assessment and Rating of Ataxia; **$SARA_{p\&g}$** = Scale for the Assessment and Rating of Ataxia posture & gait subscore; **SFW** = supervised free walking; **SPcmp** = spatial step variability compound measure; **$StrideL_{CV}$** = stride length coefficient of variation; **$StrideT_{CV}$** = stride time coefficient of variation.

Gait disturbances often present as the first signs of degenerative cerebellar ataxia (DCA)[1,2] and are one of the most disabling features throughout the disease course. It has been shown in laboratory-based assessments that measures of spatiotemporal variability allow characterization of the specificities of ataxic gait.[3–10] Moreover, they allow quantification of disease severity even at preclinical stages of DCA[11,12] and capturing of treatment-induced improvements,[13–15] thus suggesting high potential as both progression and treatment response markers in upcoming treatment trials.[16–18] Recently, studies showed that such measures characterizing ataxic gait can also be captured using wearable inertial sensors in clinical assessments.[19,20]

Wearable sensors have proven their value to capture characteristics of real-life movement in neurologic diseases like Parkinson disease[21,22] or multiple sclerosis,[23] but studies are lacking that capture ataxic gait in real life beyond the level of physical activity.[24,25]

The transfer of spatiotemporal variability measures for quantifying ataxic gait impairments into real life is complicated by the fact that real-life gait is inherently far more variable for both healthy controls and patients with cerebellar disease[26] and that patients are free to use various compensation strategies, thus increasing heterogeneity of walking patterns. Thus variability measures may lose their accuracy for characterizing ataxic gait changes in real life.

We aimed to unravel gait measures in real-life environments that allow us to quantify features inherent to ataxic gait changes, as it will be these features that will be particularly sensitive to change by upcoming treatment trials specifically targeting cerebellar dysfunction.

Methods

Standard protocol approvals, registration, and patient consents

The experimental procedure was approved by the local ethics committee (598/2011BO1). All participants gave their informed consent prior to participation.

Primary research question

The primary aim of our study was to identify gait features that allow quantification of ataxia-specific gait features in real life. The study provides Class I evidence that a set of gait variability measures, even if accessed in real life, correlated with the clinical severity of ataxia in patients with degenerative cerebellar disease.

Participants

Forty-three patients with DCA (age 51 ± 15 years) were recruited from the Ataxia Clinics of the University Hospitals Tübingen and Essen, Germany. Patients were included based on following inclusion criteria: (1) DCA in the absence of any signs of secondary CNS disease; (2) age between 18 and 75 years; (3) able to walk without walking aids. The exclusion criteria were severe visual or hearing disturbances, cognitive impairment, predominant nonataxia movement disorders (e.g., parkinsonism, spasticity), or orthopedic constraints. Severity of ataxia was rated using the Scale for the Assessment and Rating of Ataxia (SARA).[27] SARA covers a range from 0 (no ataxia) to 40 (most severe ataxia). The SARA score includes the following 8 items: 3 items rating gait and posture, 1 item for speech disturbances, and 4 items for limb-kinetic functions. The 3 items rating gait and posture are grouped by the SARA posture & gait subscore ($SARA_{p\&g}$).[11,28] The group of patients with DCA had a mean SARA score of 9.4 (range 1–16) and mean $SARA_{p\&g}$ subscore of 3.6 (range 0–6). The patient population included 2 preataxic mutation carriers for spinocerebellar ataxia types 2 and 3, respectively, with a SARA score below the threshold of 3 points.[27] For details of patient characteristics, see table 1.

We recruited 35 healthy controls (HCs; age 48 ± 15 years). HCs had no history of any neurologic or psychiatric disease, no family history of neurodegenerative disease, and did not show any neurologic signs upon clinical examination. Group sizes have been estimated based on earlier laboratory-based ataxic gait studies.[3,6,15]

Gait conditions

Walking movements were recorded in 3 different conditions: (1) laboratory-based walking (LBW condition): walking was constrained by a specified walking distance of 50 meters in a specific quiet nonpublic indoor floor within an institutional setting (hospital), and supervised by a study assessor watching the walking performance; participants were instructed to walk normally at a self-selected speed; (2) supervised free walking (SFW condition): unconstrained walking in public indoor floor and outdoor spaces in an institutional (hospital) compound

Table 1 Patient characteristics

Patient	Age, y	Sex	Diagnosis	SARA	$SARA_{p\&g}$	Strides, n, LBW	Strides, n, SFW	Strides, n, RLW
CA 1	49	F	SCA3	8.5	4	42	285	4,860
CA 2	49	F	ADCA	3	1	48	335	3,592
CA 3	37	M	ATM	8.5	3	52	322	2,321
CA 4	68	M	SAOA	13.5	5	46	136	1,112
CA 5	55	F	ADCA	8.5	3	118	296	2,060
CA 6	48	F	SCA2	1	0	48	339	4,362
CA 7	50	M	SCA3	13	6	55	183	3,354
CA 8	64	F	SAOA	13	4	55	198	2,556
CA 9	63	F	SAOA	10	5	61	246	2,022
CA 10	37	M	SPG7	16	5	66	260	1,063
CA 11	58	F	SCA14	10	4	81	304	1,011
CA 12	61	M	ADCA	10	5	90	616	2,412
CA 13	29	F	EOA	1	0	56	198	5,734
CA 14	49	M	PNPLA6	9.5	4	57	324	1,698
CA1 5	39	M	SCA1	5	1	49	313	4,359
CA 16	39	M	SCA2	7	1	44	251	5,337
CA 17	40	M	SCA3	13	5	52	444	5,078
CA 18	55	F	ADCA	13	4	60	217	2,445
CA 19	52	F	SAOA	15	6	33	226	1,141
CA 20	62	M	SCA6	12.5	4	122	436	1,907
CA 21	48	M	SCA3	1	0	65	247	5,683
CA 22	49	M	ADCA	11	5	67	—	—
CA 23	65	M	SPG7	6.5	3	59	—	—
CA 24	53	M	SCA7	14	5	102	—	—
CA 25	57	F	SCA28	11	3	54	—	—
CA 26	20	M	ADCK3	11	3	56	—	—
CA 27	57	F	SAOA	11.5	7	77	—	—
CA 28	60	F	ADCA	8.5	1	50	—	—
CA 29	41	F	ANO10	9.5	2	49	—	—
CA 30	56	F	SCA3	12.5	5	56	—	—
CA 31	39	M	SCA1	13.5	6	66	—	—
CA 32	78	F	SAOA	7.5	6	64	—	—
CA 33	46	M	SPG7	7.5	3	45	—	—
CA 34	67	M	ANO10	8.5	3	54	—	—
CA 35	74	M	ADCA	14	5	83	—	—
CA 36	35	M	SCA2	5	1	46	—	—
CA 37	31	F	EOA	11.5	4	46	—	—
CA 38	63	F	SCA1	5	2	48	—	—

Continued

Table 1 Patient characteristics *(continued)*

Patient	Age, y	Sex	Diagnosis	SARA	$SARA_{p\&g}$	Strides, n, LBW	Strides, n, SFW	Strides, n, RLW
CA 39	72	M	SAOA	9.5	4	57	—	—
CA 40	44	M	SCA1	4.5	1	44	—	—
CA 41	59	F	SCA29	8.5	3	47	—	—
CA 42	20	F	SCA29	15.5	7	56	—	—
CA 43	57	M	SAOA	6	5	69	—	—
CA		Ø 51 ± 14		Ø 9.4 ± 3.9	Ø 3.6 ± 1.9	Ø 59 ± 19	Ø 254 ± 119	Ø 3,052 ± 1,600
CA_{RLW}		Ø 50 ± 11		Ø 9.1 ± 4.7	Ø 3.3 ± 2			

Abbreviations: ADCA = autosomal dominant ataxia of still undefined genetic cause; ATM = ataxia telangiectasia; CA = cerebellar ataxia; EOA = early-onset ataxia of still undefined genetic cause; LBW = laboratory-based walking; PNPLA = patatin-like phospholipase domain containing proteins; RLW = real-life walking; SAOA = sporadic adult-onset ataxia; SCA = autosomal-dominant spinocerebellar ataxia of defined genetic type; SARA = Scale for the Assessment and Rating of Ataxia; SARAp&g = Scale for the Assessment and Rating of Ataxia posture & gait subscore; SCA = spinocerebellar ataxia; SFW = supervised free walking; SPG = spastic paraplegia.
The following diagnoses denote the gene underlying the respective ataxia type: *ATM*; *SPG7* = hereditary spastic paraplegia type 7; *SYNE1* = autosomal recessive cerebellar ataxia type 1; *SETX* = ataxia with oculomotor apraxia type 2; *ADCK3* = autosomal-recessive cerebellar ataxia type 2; *PNPLA6*, *ANO10* = autosomal-recessive SCA type 10. Clinical ataxia severity was determined by SARA.[27] SARAp&g is defined by the first 3 items of the SARA score, which capture gait, standing, and sitting.[28] Number of strides denotes the number of steps analyzed for the given walking condition.

where participants were free to choose and change the floors and indoor and outdoor spaces where they wished to walk (complete walking time: 5 minutes) with all spaces being open to the public, but still supervised by a study assessor watching the participant's walking performance; and (3) real-life walking (RLW condition): unconstrained walking during participants' everyday living where participants were free to move how they wanted and were used to in their individual daily life, without supervision by any study personnel (total recording time: 4–6 hours). Participants were instructed to wear the sensors inside and outside their house, and include at least a half-hour walk (for an overview of all conditions, see table 2). Participants documented their recorded walking movements in an activity protocol. Out of the respective total groups, 21 patients with cerebellar ataxia (CA) and 17 HCs were available for the RLW condition (for an overview of these participants, see table 1).

Movement measures

Three Opal inertial sensors (APDM, Inc., Portland, WA) were attached on both feet and posterior trunk at the level of L5 with elastic Velcro bands. Inertial sensor data were collected and wirelessly streamed to a laptop for automatic generation of gait and balance metrics by Mobility Lab software (APDM, Inc.). For the unconstrained walking conditions (SFW, RLW), data were logged on board of each Opal sensor and downloaded after the session. Selected walking bouts contained 5 subsequent strides with a minimum average velocity of 0.5 × the average walking speed in the constrained walking trail. Step events, as well as spatiotemporal gait parameters from the inertial measurement unit sensors were extracted using APDM's Mobility Lab software (Version 2),[29] which has been shown to deliver good to excellent accuracy and repeatability.[30,31] For each detected stride, the following features were extracted: stride length, stride time, lateral step deviation, and raw accelerometer data of the lumbar sensor.

Out of the rich source of possible gait measures, we chose a hypothesis-based approach selecting only those measures that were considered as promising parameter candidates in degenerative ataxia based on previous studies.[3,5–7,11,12] Variability measures were calculated using the coefficient of variation CV = σ/μ, normalizing the SD with the mean value.[32] On this basis, stride length CV ($StrideL_{CV}$) and stride time CV ($StrideT_{CV}$) were determined.

The measure of lateral step deviation (LatStepDev) was determined on the basis of 3 consecutive walking steps, calculating the perpendicular deviation of the middle foot

Table 2 Description of walking conditions

Condition	Description
Laboratory-based walking	Participants walked 50 meters straight on a 25-meter indoor floor (i.e., including one turn) at their preferred speed on a prespecified straight route in an institutional setting supervised without any distractions
Supervised free walking	Participants walked in public indoor and outdoor spaces on an institutional compound for 5 minutes at their preferred speed without prespecified route, but supervised by a study assessor
Real-life walking	Participants walked as part of their individual routine of daily living in their usual indoor and outdoor settings for 4–6 hours, without prespecified routes or supervision

placement from the line connecting the first and the third step (figure 1A). LatStepDev was normalized with stride length (% of stride length), thus providing a measure independent from stride length variability, which is suggested to be increased in real-life gait.

In order to establish a measure that captures different types of spatial step variability, we combined the measure of step length variability ($StrideL_{CV}$) (mostly anterior–posterior direction) with the measure of lateral step deviation (LatStepDev) (medio-lateral dimension). The spatial step variability compound measure SPcmp was determined in 2 steps: step 1 determines for each of the 2 parameters ($StrideL_{CV}$) and (LatStepDev) separately the relative value of an individual participant in comparison to the value range of all participants (resulting in values between 0 and 1; figure 1B). In step 2, that measure out of these 2 measures was taken for final analysis where the individual's result showed a larger abnormality (shown by a value nearer to 1), whereas the respective other measure was not entered into the further analysis (see also equation 1 and figure 1B).

$$SP_{cmp}\ (CP_i) = \max\left(\left(\frac{StrideL_{CV}\ CP_i - \min\limits_{CP+HC} StrideL_{CV}}{\max\limits_{CP+HC} StrideL_{CV} - \min\limits_{CP+HC} StrideL_{CV}}\right), \left(\frac{LatStepDev\ CP_i - \min\limits_{CP+HC} LatStepDev}{\max\limits_{CP+HC} LatStepDev - \min\limits_{CP+HC} LatStepDev}\right)\right) \quad (1)$$

In addition, harmonic ratio[33,34] of pelvis acceleration was determined to quantify the smoothness of motion. The method quantifies the harmonic content of the acceleration signals in each direction (harmonic ratio anterior-posterior [AP], medio-lateral, vertical) using stride frequency as the fundamental frequency component. Using a finite Fourier series, the components of the acceleration signal that are in phase (the even harmonics) are compared to the components that are out of phase (odd harmonics), and a harmonic ratio is calculated by dividing the sum of the amplitudes of the first 10 even harmonics by the sum of the amplitudes of the first 10 odd harmonics.[33] Thus the harmonic ratio quantifies the harmonic composition of these accelerations for a given stride where a higher harmonic ratio is interpreted as greater walking smoothness. It has been recently shown that harmonic ratio measures distinguish between patients with cerebellar disease and HCs in laboratory-based walking trails.[20,35]

Statistics

Between-group differences (CA vs HC group) of movement features were determined by the nonparametric Kruskal-Wallis test. When the Kruskal-Wallis test yielded a significant effect ($p < 0.05$), post hoc analysis was performed using a Mann-Whitney *U* test. The same tests were used to distinguish between ataxia severity subgroups, which were stratified according to the degree of gait and posture dysfunction based on the $SARA_{p\&g}$ subscore: mild (CA_{Mild}) = $SARA_{p\&g}$ 0–2; moderate (CA_{Mod}) = $SARA_{p\&g}$ 3–4; severe (CA_{Sev}) = $SARA_{p\&g}$ 5–6. Receiver operating characteristic (ROC) analysis determining the classification accuracy was used to quantify the discrimination capability of the examined measures for different walking conditions.

Repeated measurements analyses were performed using the nonparametric Friedman test (χ^2, p values) to determine within-group differences between walking conditions. When the Friedman test yielded a significant effect ($p < 0.05$), post hoc analysis was performed using a Wilcoxon signed-rank test for pairwise comparisons between assessments. We report 3 significance levels: (1) uncorrected $p < 0.05$, (2) Bonferroni-corrected for multiple comparisons $p < 0.05/n = 7$: number of analyzed features, (3) $p < 0.001$. Spearman ρ was used to examine the correlation between movement measures and SARA scores as well as between measures for different walking conditions. Effect size ρ were given with 95% confidence intervals (CIs) and were classified as ρ: 0.1 small effect, 0.3 medium effect, 0.5 large effect, 0.7 very large effect.[36,37]

To analyze the sensitivity of the movement measures to detect clinically important changes in ataxia severity, we compared gait measures for patients with (1) a difference of 1 point as well as (2) with a difference of 2 points in the $SARA_{p\&g}$ subscore. These ranges are motivated by previous analysis on the responsiveness of the SARA, showing that a change of 1 SARA point can be considered as a clinically important progression.[38] In addition, ranges are motivated by motor intervention studies demonstrating that current treatment interventions can yield an average improvement of 1.5–2 points on the $SARA_{p\&g}$ subscore, and that these effects represent patient-relevant improvements.[14,15,39,40] A Wilcoxon signed-rank test was performed to test for differences between patient groups categorized by a δ of 1 and 2 points $SARA_{p\&g}$, respectively. The effect sizes for group differences were determined by Cohen *d*[36] with pooled SDs[41] and were given with 95% CIs (Cohen $d = 0.5$–0.8 medium effect, $d > 0.8$ strong effect, $d > 1.3$ very strong effect[36]). Statistical analysis was performed using MATLAB (version 2017 B).

Data availability

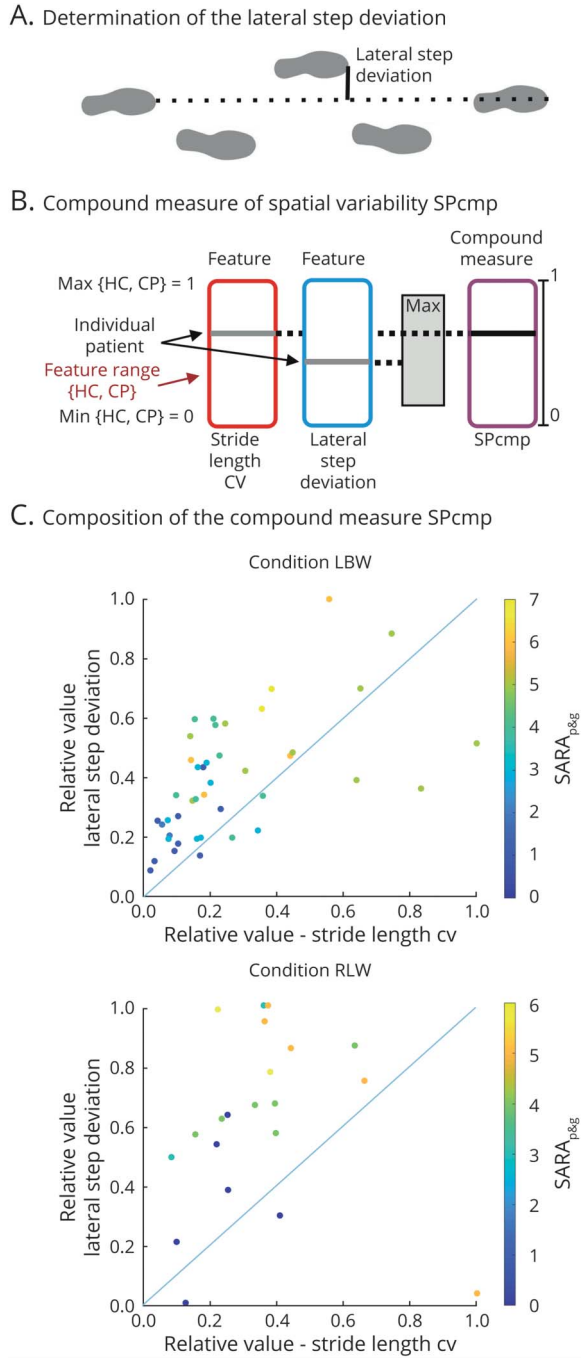
Data will be made available upon reasonable request. The data supporting the findings of this study are available within the article and its supplementary material is available from Dryad (doi:10.5061/dryad.4tmpg4f62). Raw data regarding human participants (e.g., clinical data) are not shared freely to protect the privacy of the human participants involved in this study; no consent for open sharing has been obtained.

Results

Group differences between HCs and patients with CA for different walking conditions

In the constrained walking condition (LBW, $N_{CA} = 43$), highly significant group differences ($p < 0.00014$) were observed for all measures of spatiotemporal gait variability and smoothness

Figure 1 Measurement of lateral step deviation (LatStepDev), determination of the spatial step variability compound measure (SPcmp), and composition of the SPcmp for the walking conditions laboratory-based walking (LBW) and real-life walking (RLW)



(A) Illustration of the measurement of LatStepDev. (B) Determination of the compound measure SPcmp by the maximum of the relative values for the parameters stride length coefficient of variation ($StrideL_{CV}$) and LatStepDev. (C) Composition of the compound measure SPcmp for the walking conditions LBW and RLW. Shown are the relative parameter values of each patient for the parameters $StrideL_{CV}$ (x-axis) and LatStepDev (y-axis). The color coding denotes the severity of gait and posture ataxia as determined by the Scale for the Assessment and Rating of Ataxia posture & gait subscore ($SARA_{p\&g}$) score. CV = coefficient of variation; HC = healthy control; CP = patients with cerebellar disease.

of movements (figure 2); similar LBW results were found also considering only that subgroup of patients with CA who were available also for the RLW condition ($LBW_{RLW\text{-}subgroup}$, n = 21; table B, doi:10.5061/dryad.4tmpg4f62). Also in the unconstrained walking conditions SFW and RLW, several variability measures like $StrideL_{CV}$ (p = 0.025, d = 0.82, ROC accuracy 0.75) and $StrideT_{CV}$ (p = 0.02, d = 0.86, ROC accuracy 0.72) allowed to distinguish between HC and patients with CA (figure 2 and table C, doi:10.5061/dryad.4tmpg4f62). Effect sizes and discrimination performance were smaller than in LBW, as variability in gait measures was generally higher in these unconstrained walking conditions, which was observed in both HCs and patients.

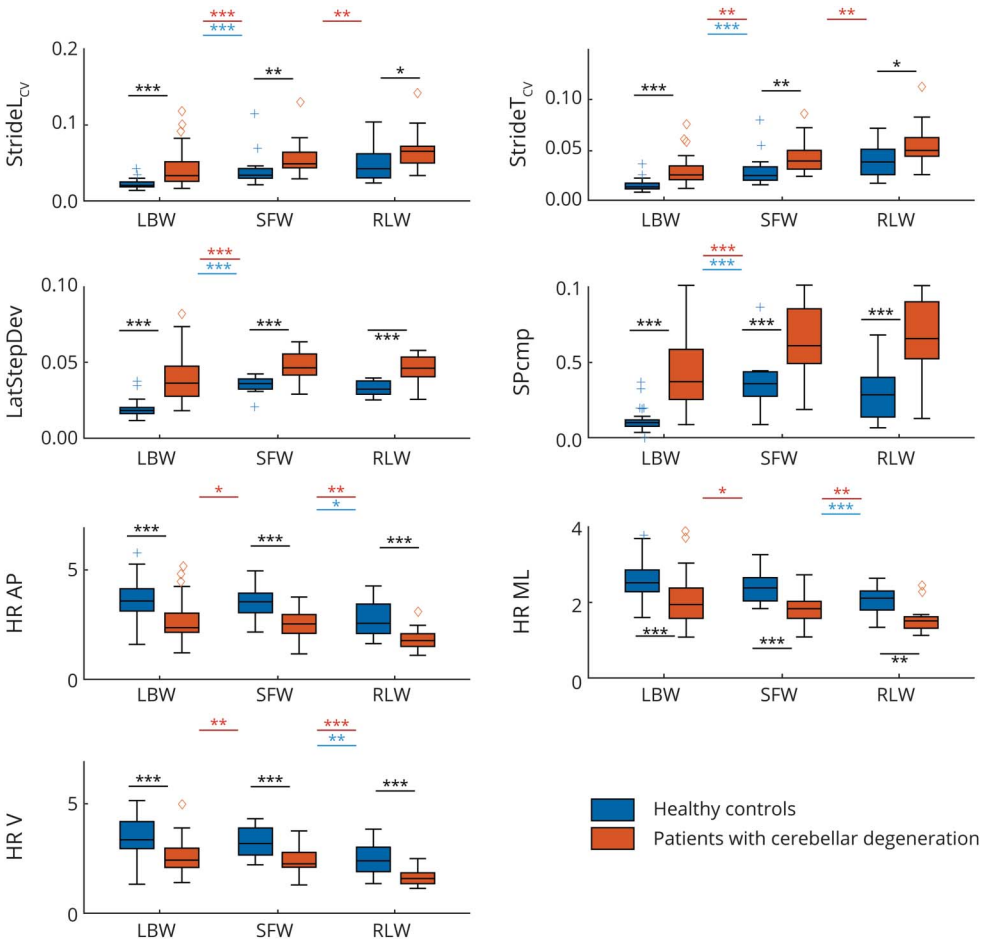
In contrast, the measures LatStepDev and SPcmp showed a similarly high effect size for both unconstrained conditions (SFW, RLW) as in the constrained condition LBW, which was observed in both patients and controls (figure 2; see blue and red asterisks for differences between conditions). These measures also showed the clearest discrimination between CA and HC in the real-life condition RLW (LatStepDev: p = 0.0002, d = 1.6, ROC accuracy 0.86; SPcmp: p = 0.00012, d = 2.6, ROC accuracy 0.86).

Sensitivity to ataxia severity in different walking conditions

Most movement measures in the constrained walking condition LBW showed a highly significant correlation with the $SARA_{p\&g}$ subscore (effect size $\rho > 0.65$), indicating a sensitivity of our measures in this condition to ataxia severity (table 3). The degree of these correlations decreased for several measures in the unconstrained walking condition SFW, and for even more measures in the real-life condition RLW, including $StrideL_{CV}$ and $StrideT_{CV}$. However, the measures LatStepDev, SPcmp, and AP harmonic ratio revealed significant correlations of high effect size with the $SARA_{p\&g}$ subscore ($p \leq 0.008$, $\rho > 0.56$) also in the real life condition RLW (table 3). See supplementary information (Inventory of Non-Ataxia Signs [INAS]; doi:10.5061/dryad.4tmpg4f62) for an analysis on the possible influence of nonataxic impairments as determined by the INAS score[42] or gait measures on our main sensor results. No substantial influence on nonataxic dysfunctions—whether determined clinically or by sensor measures—on our main parameters was observed.

In order to examine the sensitivity of the movement measures to ataxia severity in further detail, we binned the patient population in 3 subgroups: CA_{Mild} (6 participants in RLW), CA_{Mod} (7 participants in RLW), and CA_{Sev} (8 participants in RLW) according to the $SARA_{p\&g}$ subscore (see Methods). Figure 3 shows subgroup measures for the walking conditions LBW and RLW. The measures $StrideT_{CV}$ ($p < 0.006^{**}$), LatStepDev ($p < 0.02^{*}$), SPcmp ($p < 0.01^{*}$), and AP harmonic ratio ($p < 0.01^{*}$) distinguished between subgroups for constrained walking significantly (LBW). Moreover, SPcmp distinguished between subgroups in real life ($p < 0.03^{*}$), despite the small sizes of the subgroups in the RLW condition.

Figure 2 Between-group differences between patients with cerebellar disease (CA, orange) and healthy controls (HC, blue) within each of the different walking conditions



Shown are group differences for constrained laboratory-based walking (LBW), supervised free walking (SFW), and real-life walking (RLW). Black asterisks indicate significant differences between groups (*p < 0.05, **p < 0.007 Bonferroni-corrected, ***p < 0.001). Also shown are within-group differences between the different walking conditions (orange asterisks: significant differences between walking conditions in the CA cohort; blue asterisks: significant differences between walking conditions in HC). AP = anterior-posterior; HR = harmonic ratio; LatStepDev = lateral step deviation; ML = mediolateral; SPcmp = spatial step variability compound measure; StrideLCV = stride length coefficient of variation; StrideTCV = stride time coefficient of variation; V = vertical.

Sensitivity to capture clinically important differences in ataxia severity in real life

We next analyzed whether our measures allow us to detect the quantitative motor correlates of rather small but clinically important and everyday living relevant differences (see Methods and Discussion). To this end, we compared measures for patients who differ only 1 and 2 points, respectively, in the $SARA_{p\&g}$ subscore. Paired statistics revealed significant differences between these patient groups for several measures (table 4). The compound measure SPcmp yielded the largest effect sizes for the real-life condition (RLW) of $d = 0.67$ for $\Delta\ SARA_{p\&g} = 1$, and $d = 1.2$ for $\Delta\ SARA_{p\&g} = 2$. Despite smaller cohort size ($N_{LBW} = 43$, $N_{RLW} = 21$), effects sizes in the RLW condition outperform those of the LBW condition (table 4).

Relationships of movement measures across conditions and across measures

All measures of spatial and temporal variability as well as the harmonic ratios were highly correlated across all 3 conditions in patients with CA (table F, doi:10.5061/dryad.4tmpg4f62). In contrast, only few correlations were found across conditions in HCs (table G, doi:10.5061/dryad.4tmpg4f62). Similarly, close relationships across measures were observed for patients with CA, with strong correlations between harmonic ratios determining movement smoothness and spatiotemporal step variability for all walking conditions (table H, doi:10.5061/dryad.4tmpg4f62).

Discussion

This study aimed to test the hypothesis that spatiotemporal gait measures reflecting the inherent features of ataxic gait in DCA can be captured by wearable sensors not only in indoor and supervised clinical settings, but also remotely during real-life walking in everyday living. We were able to identify measures that allow us to quantify ataxia features across all of these settings with high discrimination accuracy against controls as well as with sensitivity to ataxia severity. This included in particular unconstrained real-life environments (RLW) as more complex, yet ecologically more valid settings, e.g. for future patient-centered treatment trials in DCA.

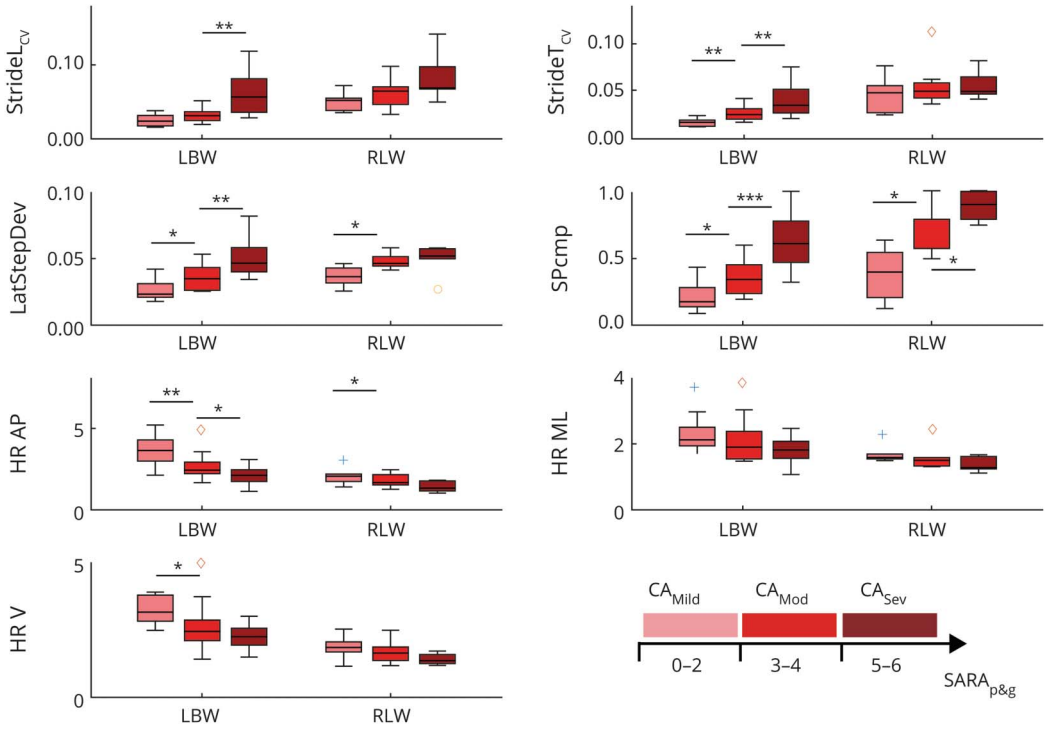
Table 3 Correlations between the Scale for the Assessment and Rating of Ataxia posture & gait subscore ($SARA_{p\&g}$) and gait measures in different walking conditions for the cohort of patients with cerebellar ataxia

	Constrained walking LBW		Free walking SFW		Real life walking RLW	
$SARA_{p\&g}$/gait measures	ρ/CIρ	*p* Value	ρ/CIρ	*p* Value	ρ/CIρ	*p* Value
Stride length variability	0.65/(0.48 to 0.78)	<0.0001[c]	0.34/(−0.05 to 0.62)	0.1	0.47/(0.13 to 0.72)	0.03[a]
Stride time variability	0.71/(0.55 to 0.82)	<0.0001[c]	0.2/(−0.16 to 0.51)	0.36	0.27/(−0.11 to 0.58)	0.24
Lateral step variability	0.75/(0.61 to 0.84)	<0.0001[c]	0.63/(0.36 to 0.8)	0.001[b]	0.63/(0.34 to 0.81)	0.0023[b]
Spatial step compound	0.78/(0.65 to 0.86)	<0.0001[c]	0.64/(0.38 to 0.81)	<0.0001[c]	0.76/(0.55 to 0.88)	0.0001[c]
Smoothness anterior-posterior harmonic ratio	−0.58/(−0.73 to −0.38)	0.0004[c]	−0.6/(−0.78 to −0.32)	0.002[b]	−0.56/(−0.7 to −0.24)	0.008[a]
Smoothness medio-lateral harmonic ratio	−0.34/(−0.55 to 0.01)	0.026[a]	−0.56/(−0.76 to −0.26)	0.0049[b]	−0.47/(−0.7 to −0.12)	0.033[a]
Smoothness vertical harmonic ratio	−0.55/(0.39 to 0.73)	0.00011[c]	−0.55/(−0.75 to −0.26)	0.0051[b]	−0.47/(−0.7 to −0.12)	0.033[a]

Abbreviations: CI = confidence interval; LBW = laboratory-based walking; RLW = real-life walking; SFW = supervised free walking.
Effect sizes of correlations are given using Spearman ρ.
[a] $p < 0.05$.
[b] $p < 0.007$ Bonferroni-corrected.
[c] $p < 0.001$.

Our findings in the constrained walking condition LBW confirm the results of previous studies from our and other groups with different movement capture technologies,[3,4,6,12,43] including wearable sensors.[19,44,45] These studies showed that spatiotemporal variability measures like stride length variability ($StrideL_{CV}$) and stride time variability ($StrideT_{CV}$) in

Figure 3 Differences between subgroups of patients with cerebellar disease stratified according to gait and posture ataxia severity as determined by the Scale for the Assessment and Rating of Ataxia posture & gait ($SARA_{p\&g}$) subscore



Subgroups: CA_{Mild}: $SARA_{p\&g}$ (0–2), CA_{Mod}: $SARA_{p\&g}$ (3–4), CA_{Sev}: $SARA_{p\&g}$ (5–6). Shown are group differences for constrained laboratory-based walking (LBW) and real life walking (RLW). AP = anterior-posterior; HR = harmonic ratio; LatStepDev = lateral step deviation; ML = mediolateral; SPcmp = spatial step variability compound measure; StrideLCV = stride length coefficient of variation; StrideTCV = stride time coefficient of variation; V = vertical.

Table 4 Differences between gait measures (*p* values, Wilcoxon signed-rank test plus effect sizes indicated by Cohen *d*) when patients differ in Scale for the Assessment and Rating of Ataxia posture & gait subscore ($SARA_{p\&g}$) by 1 ($\Delta SARA_{p\&g} = 1$) or 2 points ($\Delta SARA_{p\&g} = 2$), respectively

Walking condition	Measure	$p\Delta SARA_{p\&g} = 1$	Cohen *d*	CI_d	$p\Delta SARA_{p\&g} = 2$	Cohen' *d*	CI_d
LBW	$StrideL_{CV}$	<0.0001[c]	0.42	0.23 to 0.6	<0.0001[c]	0.78	0.58 to 0.98
	$StrideT_{CV}$	<0.0001[c]	0.38	0.2 to 0.56	<0.0001[c]	0.79	0.59 to 0.99
	LatStepDev	<0.0001[c]	0.49	0.31 to 0.68	<0.0001[c]	0.87	0.67 to 1.1
	SPcmp	<0.0001[c]	0.51	0.33 to 0.69	<0.0001[c]	0.92	0.72 to 1.1
	Harmonic ratio AP	0.0041[b]	0.23	−0.04 to 0.41	<0.0001[c]	0.81	0.61 to 1
	Harmonic ratio ML	0.088	0.15	−0.02 to 0.33	0.0001[c]	0.4	0.2 to 0.6
	Harmonic ratio V	0.011[a]	0.22	−0.04 to 0.4	<0.0001[c]	0.6	0.4 to 0.79
$LBW_{RLW:subgroup}$	$StrideL_{CV}$	0.0047[b]	0.51	0.15 to 0.87	0.0094[a]	0.78	0.24 to 1.3
	$StrideT_{CV}$	0.023[a]	0.38	0.02 to 0.74	0.015[a]	0.67	0.13 to 1.2
	LatStepDev	0.048[a]	0.28	−0.07 to 0.64	0.019[a]	0.58	0.045 to 1.1
	SPcmp	0.0087[a]	0.39	0.03 to 0.75	0.007[b]	0.74	0.2 to 1.3
	Harmonic ratio AP	0.39	0.14	−0.22 to 0.5	0.016[a]	0.69	0.15 to 1.2
	Harmonic ratio ML	0.081	0.33	−0.03 to 0.68	0.81	0.06	−0.46 to 0.59
	Harmonic ratio V	0.27	0.16	−0.17 to 0.54	0.21	0.37	0.16 to 0.89
SFW	$StrideL_{CV}$	0.096	0.28	−0.036 to 0.6	0.03[a]	0.44	0.03 to 0.84
	$StrideT_{CV}$	0.53	0.1	−0.21 to 0.42	0.18	0.29	−0.12 to 0.69
	LatStepDev	<0.0001[c]	0.49	0.17 to 0.81	0.0093[a]	0.61	0.2 to 1
	SPcmp	<0.0001[c]	0.51	0.19 to 0.83	0.0016[b]	0.65	0.24 to 1.1
	Harmonic ratio AP	0.14	0.22	−0.1 to 0.53	0.0003[c]	0.79	0.37 to 1.2
	Harmonic ratio ML	0.011[a]	0.4	0.08 to 0.72	0.0021[b]	0.59	0.18 to 1
	Harmonic ratio V	0.072	0.28	0.04 to 0.59	0.0011[b]	0.62	0.21 to 1
RLW	$StrideL_{CV}$	0.02[a]	0.42	0.065 to 0.78	0.09	0.52	0.01 to 1.1
	$StrideT_{CV}$	0.45	0.14	−0.21 to 0.5	0.76	0.09	−0.62 to 0.43
	LatStepDev	0.053	0.33	−0.03 to 0.68	0.043[a]	0.59	0.058 to 1.1
	SPcmp	<0.0001[c]	0.67	0.3 to 1	<0.0001[c]	1.2	0.6 to 1.7
	Harmonic ratio AP	0.0007[c]	0.6	0.24 to 0.96	0.034[a]	0.64	0.1 to 1.2
	Harmonic ratio ML	0.0017[b]	0.57	0.21 to 0.93	0.27	0.33	−0.2 to 0.85
	Harmonic ratio V	0.0007[c]	0.61	0.25 to 0.98	0.22	0.37	−0.16 to 0.9

Abbreviations: AP = anterior-posterior; CI = confidence interval; LBW = laboratory-based walking; ML = mediolateral; RLW = real-life walking; SFW = supervised free walking; SPcmp = spatial step variability compound measure; $StrideL_{CV}$ = stride length coefficient of variation; $StrideT_{CV}$ = stride time coefficient of variation; V = vertical.
Shown are results from all walking conditions LBW, SFW, and RLW as well as for LBW with the subgroup of patients who were also available for the RLW condition ($LBW_{RLW\text{-}subgroup}$).
[a] $p < 0.05$.
[b] $p < 0.007$ Bonferroni-corrected.
[c] $p < 0.001$.

constrained walking serve as reliable and valid measures for cerebellar ataxia and—as demonstrated here for wearable sensors—correlate well with gait and posture ataxia severity. Moreover, first studies using wearable sensors have indicated that gait analysis might be more responsive to 1-year ataxia progression changes than the SARA score.[45] Taken together with our current observations, these findings are important as they confirm that measures of spatiotemporal variability deliver consistent, reproducible results in patients with ataxia across methods and centers,

as warranted for upcoming multicenter natural history and treatment trials in DCA.

Our findings add additional promising measures for ataxic gait, with LatStepDev and SPcmp showing higher effect sizes and discrimination accuracy of DCA against controls than the aforementioned previous measures (which was observed also for the constrained walking condition LBW). In addition, harmonic ratios representing measures of trunk movement smoothness—initially used in Parkinson disease[46] and multiple sclerosis[47] and more recently also in CA[20,35]—show high sensitivity for ataxia severity in constrained movements, indicating their value as novel measures quantifying ataxic gait.

We observed an increased within-group spatiotemporal variability of the measures $StrideL_{CV}$ and $StrideT_{CV}$ in both HCs and patients with CA in real-world walking (condition RLW) compared to supervised constrained walking in a clinical setting (condition LBW) (figure 2). This observation, which is consistent with previous work confined to healthy participants so far,[26] can be explained by increased voluntary variation of step length in real-life gait behavior.

This increased spatiotemporal variability in real life led to a decrease in effect size and discrimination accuracy for common measures of step variability like $StrideL_{CV}$ and $StrideT_{CV}$ in the group comparison of patients with CA compared to HCs (table C + E, doi:10.5061/dryad.4tmpg4f62). Yet large effect sizes and discrimination accuracies even in the real-life condition were revealed for the measure LatStepDev and the new compound measure SPcmp, with high similarity of these measures across conditions. This indicates that LatStepDev and SPcmp may capture a more condition-independent, i.e., robust ataxia component of spatiotemporal variability, than $StrideL_{CV}$ and $StrideT_{CV}$.

The measures LatStepDev and SPcmp as well as AP and vertical harmonic ratios did not only allow to us distinguish patients with CA from healthy controls in real life; they were also highly correlated to clinical ataxia severity in this condition (table 3). Whereas harmonic ratios, $StrideL_{CV}$, and $StrideT_{CV}$ failed to reach significance for differentiating the 3 severity subgroups of patients with CA for the real-life condition RLW, LatStepDev and SPcmp were sensitive to distinguish these severity subgroups also during real-life walking (figure 3). The compound measure SPcmp seems to benefit from capturing different compensation strategies used in diverse stages of disease, and might allow to us capture gait ataxia in particular in more advanced disease stages (figure 1C).

To serve as progression and treatment outcome measures, measures of real-life walking should ideally be able to capture changes that correspond to clinically and everyday living important differences as well as to treatment effects achievable by current and future ataxia treatment interventions. A change of 1 point in the SARA score has been shown to reflect a clinically important difference over 1 year disease course,[38] determined by the patient's global impression of change using quality of life outcomes.[48] Moreover, changes of 1.5–2 points in the $SARA_{p\&g}$ subscore reflect treatment effect sizes consistently achieved by currently available motor rehabilitation interventions.[14,15,39,40] Our measure SPcmp yields a strong effect size (Cohen $d = 1.2$) for differentiating movement patterns when patients differ by 2 $SARA_{p\&g}$ points, and an at least moderate effect size (Cohen $d = 0.67$) when patients differ by 1 $SARA_{p\&g}$ point, demonstrating that this measure is able to capture clinically important differences. Remarkably, for both types of clinically important differences ($\Delta\ SARA_{p\&g} = 1$; $\Delta\ SARA_{p\&g} = 2$), the highest effect sizes were observed in the real-life condition RLW (table 4), despite the general increase of variability in real time walking. This observation might be explained by the larger amount of walking strides available for analysis in this condition and, in addition, by the particular movement characteristics of unconstrained walking. In contrast, a shorter unconstrained trial—like the condition SFW, which comprised only 5 minutes walking—does not seem to yield equally large effect sizes. This observation is important as outcome measures with higher effect sizes—as observed here for the real-life walking condition—may reduce the sample sizes required in natural history studies and upcoming treatment trials in hereditary ataxias using, e.g., antisense oligonucleotides.[16–18] This notion, which is so far based only on cross-sectional findings, warrants further confirmation by longitudinal studies.

Despite the general increase of variability in real-life walking, we observed high correlations between the constrained laboratory-based (LBW) and the unconstrained (SFW, RLW) walking conditions. This suggests that the laboratory-based assessment might be exploited to deliver first surrogate snapshots of patients' unconstrained gait performance. However, as noted above, at least some of the measures seemed to yield larger effect sizes in real-life walking. Moreover, our current analysis of real-life walking behavior was limited to walking bouts of minimal 5 subsequent strides (rather than analysis of more complex everyday living walking behaviors), which might explain the good correlations with the constrained walking conditions. However, real life includes a much larger variety of walking movements, for instance turning movements or initiation and termination of gait, known to be demanding for dynamic balance control and impaired in cerebellar disease. To include these movements in future analyses of real-life walking behavior is highly warranted in order to capture ecological validity in even more depth.

Future studies should comprise larger DCA patient cohorts allowing subgroup analysis according to genetic disease type or comorbid nonataxic motor impairment (as, e.g., in spastic ataxias). Our study, in contrast, focused on the identification of features that robustly characterize ataxic-specific motor impairments in real life across different types of DCA.

This study unravels measures that allow quantification of real-life ataxic gait and reflect disease severity, thus yielding promising ecologically valid outcome measure candidates for future

natural history and treatment trials in DCAs. For both types of trials, measuring real-life movements bears several other advantages—in addition to the higher effect sizes gained from real-life assessments, likely caused by larger amount of sampled walking strides. These advantages include objective quantitative measurement of (1) day-to day variability instead of snapshot evaluations weeks or months apart during clinical visits[49] and (2) patients' real-world motor performance instead of partly artificial motor tasks of clinical scores or laboratory conditions, which serve as surrogate parameters at best. While assessment of constrained tasks—like in the SARA score or similar task selections at patients' homes—represents patients' real-world functioning only in a limited fashion,[50] measures of real-life motor performance add ecological validity and can thus help to inform upcoming treatment trials in DCAs and Food and Drug Administration approval of novel treatments.

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Disclosure

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Jens Seemann, MSc	Hertie Institute for Clinical Brain Research, Tübingen, Germany	Execution of the study, analysis and interpretation of the data, revising the manuscript
Martin Giese, PhD	Hertie Institute for Clinical Brain Research, Tübingen, Germany	Interpretation of the data, revising the manuscript
Andreas Traschütz, MD, PhD	Hertie Institute for Clinical Brain Research, Tübingen, Germany	Organization of the study, interpretation of the data, revising the manuscript
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Dagmar Timmann, MD	University of Duisburg-Essen, Germany	Organisation of the study, interpretation of the data, revising the manuscript
Matthis Synofzik, MD	Hertie Institute for Clinical Brain Research, Tübingen, Germany	Design and conceptualization of the study, interpretation of the data, drafting the manuscript

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Real-life gait assessment in degenerative cerebellar ataxia: Toward ecologically valid biomarkers

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