

BRIEF REPORT

Digital Gait Biomarkers Allow to Capture 1-Year Longitudinal Change in Spinocerebellar Ataxia Type 3

Winfried Ilg, PhD,^{1,2*} Björn Müller, MSc,¹ Jennifer Faber, MD,^{3,4} Judith van Gaalen, MD,⁵ Holger Hengel, MD,^{2,6} Ina R. Vogt, MD,⁴ Guido Hennes, MD,⁵ Bart van de Warrenburg, MD,⁵ Thomas Klockgether, MD,^{3,4} Ludger Schöls, MD,^{2,6} Matthis Synofzik, MD,^{2,6} and the ESMI Consortium

¹Section Computational Sensomotorics, Hertie Institute for Clinical Brain Research, Tübingen, Germany ²German Center for Neurodegenerative Diseases (DZNE), Tübingen, Germany ³Department of Neurology, University Hospital Bonn, Bonn, Germany ⁴German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany ⁵Department of Neurology, Donders Institute for Brain, Cognition, and Behaviour, Radboud University Medical Center, Nijmegen, the Netherlands ⁶Department of Neurodegeneration, Hertie Institute for Clinical Brain Research and Centre of Neurology, Tübingen, Germany

ABSTRACT: Measures of step variability and body sway during gait have shown to correlate with clinical ataxia severity in several cross-sectional studies. However, to serve as a valid progression biomarker, these gait measures have to prove their sensitivity to robustly capture longitudinal change, ideally within short time frames (eg, 1 year). We present the first multicenter longitudinal gait analysis study in spinocerebellar ataxias. We performed a combined cross-sectional ($n = 28$) and longitudinal (1-year interval, $n = 17$) analysis in Spinocerebellar Ataxia type 3 subjects (including seven preataxic mutation carriers). Longitudinal analysis showed significant change in gait measures between baseline and 1-year follow-up, with high effect sizes (stride length variability: $P = 0.01$, effect size $r_{\text{prb}} = 0.66$;

lateral sway: $P = 0.007$, $r_{\text{prb}} = 0.73$). Sample size estimation for lateral sway indicates a required cohort size of $n = 43$ for detecting a 50% reduction of natural progression, compared with $n = 240$ for the clinical ataxia score Scale for the Assessment and Rating of Ataxia (SARA). These measures thus present promising motor biomarkers for upcoming interventional studies. © 2022 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society

Key Words: gait; spinocerebellar ataxia; SCA3; motor biomarker; longitudinal analysis

With disease-modifying drugs on the horizon for degenerative ataxias,¹⁻³ sensitive motor biomarkers are highly warranted. Gait measures including step variability and body sway have shown their sensitivity to ataxia severity in multiple cross-sectional studies, correlating with clinical ataxia scores.⁴⁻¹⁶ However, such correlations are strongly influenced by the range of disease severity¹⁷: for cohorts that encompass a wide range of disease stages, many gait measures, including unspecific ones like speed, show correlation to disease severity, often predominantly driven by subjects at the ends of the spectrum of disease severity.¹⁷ In interventional trials, the goal of assessing motor biomarkers is qualitatively different, namely, the quantification of individual change in short time frames (eg, 1 year).

To serve as valid progression biomarkers, these gait measures thus have to prove their sensitivity to individual longitudinal change in a time span realistic for intervention trials. In this article, we present a first longitudinal study in a multicenter spinocerebellar ataxia (SCA) cohort. We demonstrate that digital-motor biomarkers allow to capture longitudinal change within 1-year follow-up, with this sensitivity to change outperforming clinical ataxia scores.

Subjects and Methods

Patients

The study cohort was part of the European Spinocerebellar ataxia type 3 (SCA)/Machado-Joseph disease initiative (ESMI), a multicenter prospective observational study. Twenty-eight mutation carriers of Spinocerebellar Ataxia type 3 (SCA3) were recruited from the Ataxia Clinics of the University Hospitals Tübingen and Nijmegen, as well as the German Center for Neurodegenerative Diseases in Bonn. Patients were

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](#) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

*Correspondence to: Dr. Winfried Ilg, Section Computational Sensomotorics, Hertie Institute for Clinical Brain Research, Otfried-Müller-Straße 25, 72076 Tübingen, Germany; E-mail: winfried.ilg@uni-tuebingen.de

Received: 14 March 2022; Revised: 15 July 2022; Accepted: 10 August 2022

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.29206

included based on the following inclusion criteria: (1) genetically confirmed SCA3 in the absence of any signs of secondary central nervous system disease, (2) aged 18–75 years, and (3) able to walk without walking aids. The exclusion criteria were severe visual or hearing disturbances, cognitive impairment, or orthopedic constraints. Subjects comprised 21 subjects at the ataxic stage as defined by a Scale for the Assessment and Rating of Ataxia (SARA)¹⁸ score ≥ 3 (subgroup SCA3_{ATX}), and 7 subjects at the preataxic stage (SARA score < 3) (subgroup SCA3_{PRE}). Neurological signs other than ataxia were assessed by the Inventory of Non-Ataxia Signs (INAS).¹⁹ Healthy control subjects ($n = 13$) comprised mutation-negative first-degree relatives of SCA3 carriers and unrelated healthy individuals, all without signs of neurodegenerative disease on clinical examination. See Supporting Information Supplement S1 for study population characteristics.

The study was approved by the local institutional review boards of all participating centers. Written informed consent was obtained from all study participants before enrolment.

Gait Assessment

Gait was recorded at each study site by a multi-Kinect recording system with six cameras (for a detailed description, see Supplement S2 and Muller et al.²⁰). In a previous validation study,²⁰ this system was shown to deliver good-to-excellent accuracy in several gait measures, including step length and step duration. We assessed gait in two conditions: preferred speed and slow speed. The slow speed condition was included based on previous studies demonstrating increased step variability and body sway for slow gait.²¹ In both conditions, subjects walked in their everyday-life shoes a 10-m distance for five trials. Subjects first performed walking trials with preferred speed, followed by trials with slow speed. Of all potential gait parameters, we chose a hypothesis-based approach focusing on measures that were considered promising candidates in degenerative ataxia based on previous studies,^{4,11,14,16,22} namely, measures on step variability and lateral body sway. Variability measures were calculated using the coefficient of variation (CV) = σ/μ , normalizing the standard deviation with the mean value.²³ As measures of step variability, stride length CV (StrideL_{CV}) and stride time CV (StrideT_{CV}) were determined. Lateral body sway was defined as the medial-lateral component of the path of the sternum marker (see Supplement S2), normalized by the anterior-posterior component.¹⁰

Statistics

Between-group differences were determined by the nonparametric Kruskal–Wallis test, and post hoc analysis was performed using a Mann–Whitney *U* test.

Effects sizes were determined by Cliff's delta.²⁴ Repeated measurements analyses were performed for longitudinal analyses using the nonparametric Friedman test to determine within-group differences between assessments, and post hoc analysis was performed using a Wilcoxon signed-rank test. Effect sizes for the repeated measurements were determined by matched-pairs rank biserial correlation.²⁵ Estimated time to ataxia onset was calculated based on the individual's CAG repeats, as described by Tezenas du Montcel et al.²⁶ We report three significance levels: (1) uncorrected $*P < 0.05$; (2) Bonferroni-corrected for multiple comparisons $**P < 0.05/n$, with $n = 6$ analyzed gait features; and (3) $***P < 0.001$. Spearman's ρ was used to examine the correlation between gait measures and SARA scores. Statistical analysis was performed using MATLAB (Version R2020B). Based on the longitudinal changes, a sample size estimation was performed using G*power 3.1²⁷ to determine the required cohort size for different levels of reduction of natural progression by a hypothetical intervention.

Results

Correlation of Gait Measures to Cross-Sectional Ataxia Severity

Cross-sectional analysis showed group differences between SCA3 and HCs in all examined gait measures in both walking conditions (eg, lateral sway in preferred speed: $P = 0.00011$; slow speed: $P = 0.003$; Table 1, Fig. 1A). Step variability measures and lateral sway showed a relationship to cross-sectional ataxia severity in both walking conditions, with highest effect sizes for stride length_{CV} ($\delta = 0.64$; Table 1). For slow walking, step variability measures ($P = 0.016$) and lateral sway ($P = 0.043$) also correlated with SARA in the subgroup of ataxic SCA3 subjects (SCA3_{ATX}).

Correlations with the CAG-repeat-based estimated time to disease onset for the SCA3 group are shown in Supplement S3.

Sensitivity of Gait Measures to Longitudinal Change after 1 Year

We next analyzed whether gait measures allow to detect longitudinal changes at 1-year follow-up assessment (duration: 377 ± 33 days). Follow-up data were available from 17 subjects SCA3^{FU} (10 ATX, 7 PRE). Reasons for dropout from longitudinal recording were unavailability ($n = 6$), technical problems ($n = 4$), and disability in walking without aids at follow-up because of disease progression ($n = 1$).

Although the SARA ($P = 0.2$, effect size $r_{prb} = 0.27$) and the INAS ($P = 0.125$, $r_{prb} = 0.4$) failed to detect longitudinal change (Table 1), paired statistics demonstrated differences between baseline and follow-up in

TABLE 1 Results of cross-sectional and longitudinal analyses

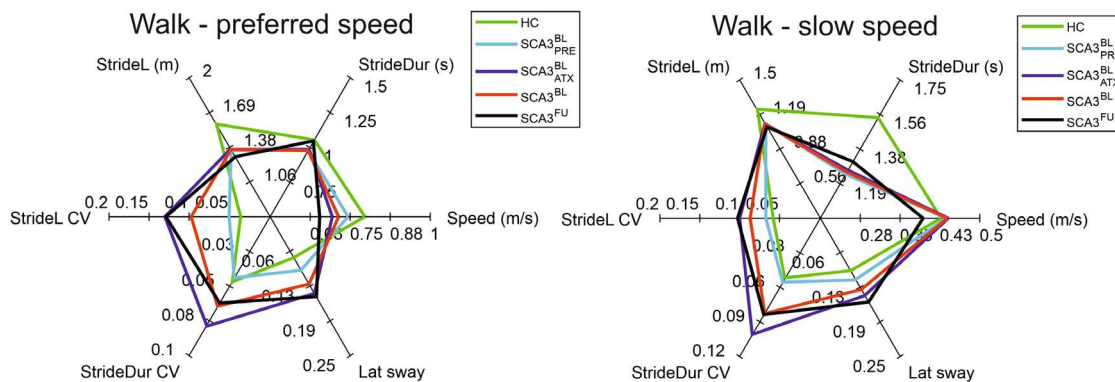
	Cross-sectional analyses						Longitudinal analysis			
	Group difference SCA3 vs. HCs		Correlations SCA3				SCA3 ^{BL}	SCA3 ^{FU}	Within-group difference SCA3 ^{BL} vs. SCA3 ^{FU}	
			SARA		SARA _{p&g}					
			ρ	P	ρ	P				
	P	δ	ρ	P	ρ	P	mean $\pm$ SD	mean $\pm$ SD	P	r_{prb}
Clinical scores										
SARA	0.0001***	0.77	—	—	—	—	5.32 $\pm$ 4.73	5.91 $\pm$ 4.91	0.2	0.27
SARA _{p&g}	0.0002***	0.69	—	—	—	—	2.12 $\pm$ 2.2	2.47 $\pm$ 2.43	0.125	0.40
INAS	—	—	—	—	—	—	2.31 $\pm$ 1.53	2.81 $\pm$ 2.19	0.138	0.44
Walk—preferred speed										
Speed	0.01*	0.49	0.49	0.008**	0.43	0.023*	0.74 $\pm$ 0.1	0.656 $\pm$ 0.16	0.02*	0.62
Stride duration CV	0.10	0.32	0.18	0.36	0.33	0.084	0.064 $\pm$ 0.06	0.062 $\pm$ 0.02	0.26	0.32
Stride length CV	0.04*	0.4	0.54	0.003**	0.64	0.0003***	0.097 $\pm$ 0.1	0.129 $\pm$ 0.11	0.06	0.5
Lateral sway	0.0011 **	0.67	0.26	0.19	0.27	0.17	0.12 $\pm$ 0.06	0.144 $\pm$ 0.07	0.01*	0.68
Walk—slow speed										
Speed	0.8	0.08	0.9	<0.0001	0.9	<0.0001***	0.43 $\pm$ 0.1	0.39 $\pm$ 0.12	0.03*	0.6
Stride duration CV	0.02*	0.48	0.5	0.007**	0.45	0.016*	0.08 $\pm$ 0.03	0.1 $\pm$ 0.04	0.63	0.17
Stride length CV	0.015*	0.52	0.46	0.014*	0.53	0.004**	0.087 $\pm$ 0.03	0.103 $\pm$ 0.04	0.01*	0.66
Lateral sway	0.003 **	0.63	0.54	0.002**	0.52	0.021*	0.128 $\pm$ 0.03	0.151 $\pm$ 0.04	0.007**	0.73

Cross-sectional analyses: between-group differences of healthy control subjects (HCs) and SCA3 subjects for clinical measures and gait measures in the walking conditions with preferred and slow speed. δ denotes the effect sizes determined by Cliff's delta. Correlations between gait measures and clinical ataxia severity (SARA total score, SARA_{p&g} posture and gait subscore) are given for the SCA3 group. The three items of the SARA assessing gait and posture (gait, stance, sitting) were grouped by the subscore SARA posture and gait (SARA_{p&g}).^{21,35} Effect sizes of correlations are given using Spearman's ρ . Longitudinal analyses of 1-year follow-up assessments: paired statistics for within-subject comparisons of clinical scores and gait measures for the two walking conditions (P values, Wilcoxon signed-rank test; effect sizes r_{prb} determined by matched pairs rank biserial correlation²⁴). Shown are analyses for the group of SCA3 subjects at baseline (SCA3^{BL}) and 1-year follow-up (SCA3^{FU}).

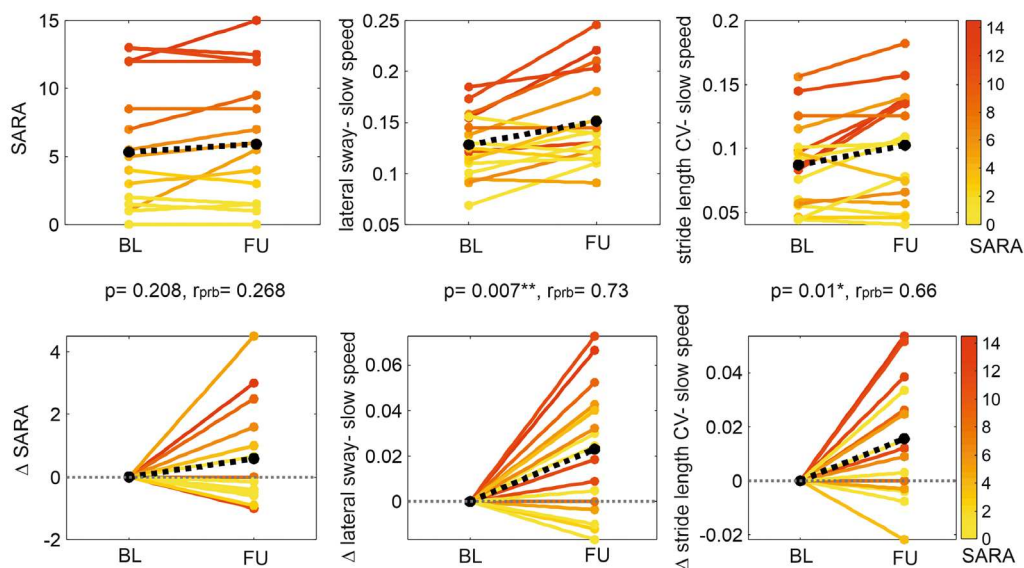
* $P < 0.05$, ** $P < 0.0083$ Bonferroni-corrected, *** $P < 0.001$. Asterisks indicate significant differences between groups.

HC, healthy control subject; SARA, Scale for the Assessment and Rating of Ataxia; SCA3, Spinocerebellar Ataxia type 3; SD, standard deviation; INAS, Inventory of Non-Ataxia Signs; CV, coefficient of variation.

A Cross-sectional and longitudinal differences in gait patterns



B SCA3 1-year progression of SARA and gait parameters



C Sample size estimation for future intervention trials

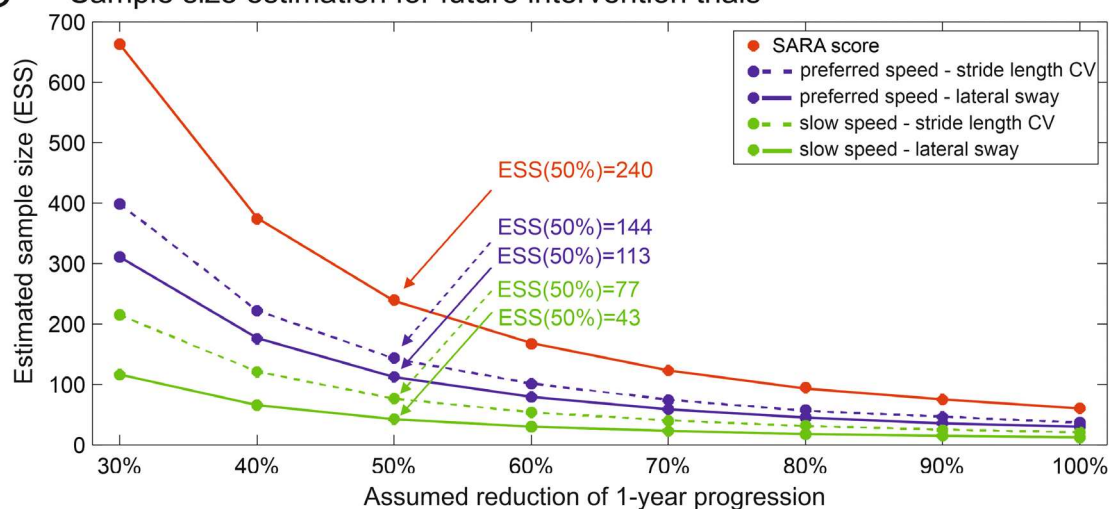


FIG. 1. Legend on next page.

gait measures for both walking conditions (preferred speed: lateral sway, $*P = 0.01$, $r_{prb} = 0.68$; slow speed: lateral sway, $*P = 0.007$, $r_{prb} = 0.73$, stride_{LCV}: $*P = 0.01$, $r_{prb} = 0.66$; Table 1, Fig. 1A,B).

Given the highest effect size, lateral sway was selected for sample size calculation. For detecting a 50% reduction of natural progression by a hypothetical intervention (95% power and one-sided 5% type I error), $n = 43$ subjects would be required if taking the lateral sway during slow walking as primary outcome measure, compared with $n = 240$ subjects if taking the SARA as primary outcome measure (Fig. 1C).

Subgroup analyses showed even higher effect sizes to longitudinal change for the ataxic SCA3 subgroup SCA3_{ATX}^{FU} (preferred speed: lateral sway, $*P = 0.03$, $r_{prb} = 0.74$; slow speed: lateral sway, $*P = 0.01$, $r_{prb} = 0.87$), indicating that the high sensitivity to change is predominantly driven by the ataxic subjects SCA3_{ATX} (Supplement S4).

Discussion

Gait disturbance often presents as the first sign of cerebellar ataxia^{28,29} and is one of the most disabling features throughout the disease course, thus suggesting a high potential as both progression and response marker in upcoming treatment trials.^{1,2,30}

This study aimed to test the sensitivity of gait measures to capture longitudinal change within 1 year in a SCA3 and a multicenter setting. Analyses demonstrated that gait measures (1) correlate with cross-sectional clinical ataxia severity, thus indicating valid capture of clinical ataxia dysfunction; and in particular, (2) capture longitudinal change between baseline and 1-year follow-up with high effect sizes, hereby substantially outperforming clinical ataxia scales.

Gait Measures Are Sensitive to Cross-Sectional Ataxia Severity

Gait variability measures have proved cross-sectional sensitivity to ataxia severity in a wide range of recording methods,^{31,32} including marker-based capturing systems as gold standard,^{10,11,22} gait mattresses,^{14,21}

wearable sensors,^{5,6,8,9} and camera-based systems,⁷ like the multi-Kinect system.²⁰

Our results validate these findings in a multicenter setting and in an early-stage SCA3 cohort (low SARA score with mean 8.1 points), thus demonstrating their applicability to early disease stages of SCA, as targeted by upcoming interventional studies.

Gait Measures Capture Longitudinal Change Within 1 Year

It is key for upcoming interventional trials that sensitivity to change of these gait markers is proved by quantification of individual changes in short, trial-like time frames. For upcoming disease-modifying drugs in SCA, the main outcome will be slowing of disease progression in a limited study period, ideally capturable already within, eg, 1 year.

Our SCA3 cohort presents a paradigmatic example for upcoming interventions because SCA3 is the globally most frequent SCA genotype with relatively fast progression,^{33,34} and interventional trials are expected still in 2022. In our cohort, we observed a smaller annual change in the SARA score than reported for SCA3 in earlier studies^{33,34} (0.6 vs. 1.56 in Jacobi et al.³³), which is most probably due to the earlier disease stage in our study (mean SARA 5.57 vs. 14.1 in Jacobi et al.³³), thus also representing better the disease strata included in upcoming trials.

Although annual change in the ataxia score (SARA) or in nonataxia items (INAS) did not reach significance (Table 1), gait measures captured progression in stride length variability and lateral body sway in both walking conditions, especially in slow walking. The large effect sizes led to substantially reduced sample size estimations in comparison with the SARA for the detection of decreased disease progression within 1 year (Fig. 1C). This reduction in sample size is actually decisive whether a trial is feasible at all: although trials with, eg, 240 SCA3 subjects (as required for SARA as outcome) are almost not possible, 43 SCA3 subjects (as required for the gait biomarker lateral sway) are well feasible.

Limitations of the Study

Our findings are limited by the relatively small cohort size. In particular, our study cohort was not sufficiently

FIG. 1. (A) Radar plots illustrating cross-sectional and longitudinal differences on six gait parameters for the two gait conditions with preferred speed and slow speed: gait speed, stride duration (StrideDur), stride length (StrideL), stride length variability (StrideL-CV), stride duration variability (StrideDur-CV), and lateral sway (Lat sway). Cross-sectional differences can be seen by comparison of healthy controls (HCs, green), the subgroup of SCA3 preataxic mutation carriers (SCA3_{PRE}^{BL}, light blue), ataxic mutation carriers (SCA3_{ATX}^{BL}, purple), as well as the group of SCA3 subjects (SCA3^{BL}, red). Given are average values for each group. Longitudinal 1-year progression can be seen comparing SCA3 subjects at baseline (BL; SCA3^{BL}, red) and 1-year follow-up (FU; SCA3^{FU}, black). **(B)** Longitudinal analyses of 1-year FU assessments: within-subject changes between BL and 1-year FU for the group of SCA3 subjects. Upper panel: within-subject changes of the SARA score and the gait measures lateral sway and stride length coefficient of variability in the slow walking condition at BL and 1-year FU. Lower panel: within-subject changes between BL and 1-year FU represented as delta (Δ). In all panels, SARA scores of individual cerebellar subjects are color coded. Black dotted line = mean change across all subjects. Asterisks indicate significant differences between time points ($*P < 0.05$, $**P < 0.0083$ Bonferroni-corrected, $***P < 0.001$). Effect sizes r_{prb} were determined by matched-pairs rank biserial correlation. **(C)** Sample size estimations were performed for future intervention trials showing different levels of reduction in progression levels for the different outcome measures: SARA, lateral sway, and stride length variability in the walking conditions with preferred and slow speed. The estimated number of subjects per study arm is plotted over the assumed therapeutic effect for lowering the 1-year progression in SCA3 subjects. [Color figure can be viewed at wileyonlinelibrary.com]

powered for detecting longitudinal change within the preataxic group only. Thus, larger future studies are needed, including a higher number of preataxic subjects, to further validate the promises of gait measures and relate longitudinal gait changes to patient-centered outcomes and patient-meaningful aspects of health,³⁵ as well as to corresponding changes in molecular (blood neurofilament light chain³⁶) and imaging biomarkers.³⁷

In future multicenter studies, the gait measures identified in this study could be assessed not by a stationary analysis setup, but rather by wearable inertial sensors.^{5,6,9} Cross-sectional studies using such inertial sensors have confirmed high sensitivity to ataxia severity for various gait variability measures as used in this study, both in clinical gait assessment^{5,6,9} and in real-life recordings,⁵ the latter being particularly important to demonstrate ecological relevance.^{5,38,39}

This also allows to capture ataxia-related impairments in real-life walking behavior, including movement components with higher demands on dynamic balance such as turnings³⁹ in addition to episodes of straight walking.

Conclusion

Our study demonstrates that digital gait measures allow to capture natural progression in SCA3 within just 1 year, with effect sizes outperforming clinical rating scales as the main established outcome measures in the field. They thus present promising motor biomarkers for upcoming SCA intervention studies. ■

Acknowledgments: This work was supported by the European Joint Programme of Neurodegenerative Diseases (JPND) and the European Union Horizon 2020 innovation program under grant agreement 643417 (ESMI) and by the European Joint Programme on Rare Diseases under the EJP RD Cofund-EJP 825575 (PROSPAX, German Research Foundation) and 441409627 (to M.S. and B.v.d.W.). B.v.d.W., T.K., L.S., and M.S. are members of the European Reference Network for Rare Neurological Diseases Project ID 739510. J.F. is a fellow within the Hertie Network of Excellence in Clinical Neuroscience Open Access funding enabled and organized by Projekt DEAL.

Data Availability Statement

Data will be made available upon reasonable request and as patient consent allows.

References

- Ashizawa T, Oz G, Paulson HL. Spinocerebellar ataxias: prospects and challenges for therapy development. *Nat Rev Neurol* 2018;14(10):590–605.
- Scoles DR, Pulst SM. Antisense therapies for movement disorders. *Mov Disord* 2019;34(8):1112–1119.
- Klockgether T, Ashizawa T, Brais B, et al. Paving the way toward meaningful trials in ataxias: an ataxia global initiative perspective. *Mov Disord* 2022;37(6):1125–1130. <https://doi.org/10.1002/mds.29032>.
- Ilg W, Golla H, Thier P, Giese MA. Specific influences of cerebellar dysfunctions on gait. *Brain* 2007;130(3):786–798.
- Ilg W, Seemann J, Giese M, et al. Real-life gait assessment in degenerative cerebellar ataxia: toward ecologically valid biomarkers. *Neurology* 2020;95(9):e11199–e1210.

- Shah VV, Rodriguez-Labrada R, Horak FB, et al. Gait variability in spinocerebellar ataxia assessed using wearable inertial sensors. *Mov Disord* 2021;36(12):2922–2931.
- Summa S, Tartarisco G, Favetta M, et al. Validation of low-cost system for gait assessment in children with ataxia. *Comput Methods Programs Biomed* 2020;196:105705.
- Velazquez-Perez L, Rodriguez-Labrada R, Gonzalez-Garcés Y, et al. Prodromal spinocerebellar ataxia type 2 subjects have quantifiable gait and postural sway deficits. *Mov Disord* 2021;36(2):471–480.
- Zhou H, Nguyen H, Enriquez A, et al. Assessment of gait and balance impairment in people with spinocerebellar ataxia using wearable sensors. *Neurol Sci* 2022;43(4):2589–2599. <https://doi.org/10.1007/s10072-021-05657-6>
- Ilg W, Schatton C, Schicks J, Giese MA, Schols L, Synofzik M. Video game-based coordinative training improves ataxia in children with degenerative ataxia. *Neurology* 2012;79(20):2056–2060.
- Ilg W, Christensen A, Mueller OM, Goericke SL, Giese MA, Timmann D. Effects of cerebellar lesions on working memory interacting with motor tasks of different complexities. *J Neurophysiol* 2013;110(10):2337–2349.
- Serrao M, Pierelli F, Ranavolo A, et al. Gait pattern in inherited cerebellar ataxias. *Cerebellum* 2012;11(1):194–211.
- Wuehr M, Schniepp R, Ilmberger J, Brandt T, Jahn K. Speed-dependent temporospatial gait variability and long-range correlations in cerebellar ataxia. *Gait Posture* 2013;37(2):214–218.
- Rochester L, Galna B, Lord S, Mhiripiri D, Eglon G, Chinnery PF. Gait impairment precedes clinical symptoms in spinocerebellar ataxia type 6. *Mov Disord* 2014;29(2):252–255.
- Hickey A, Gunn E, Alcock L, et al. Validity of a wearable accelerometer to quantify gait in spinocerebellar ataxia type 6. *Physiol Meas* 2016;37(11):N105–N117.
- Schniepp R, Wuehr M, Schlick C, et al. Increased gait variability is associated with the history of falls in patients with cerebellar ataxia. *J Neurol* 2014;261(1):213–223.
- Janse RJ, Hoekstra T, Jager KJ, et al. Conducting correlation analysis: important limitations and pitfalls. *Clin Kidney J* 2021;14(11):2332–2337.
- Schmitz-Hübsch T, du Montcel ST, Baliko L, et al. Scale for the assessment and rating of ataxia: development of a new clinical scale. *Neurology* 2006;66(11):1717–1720.
- Schmitz-Hübsch T, Coudert M, Bauer P, et al. Spinocerebellar ataxia types 1, 2, 3, and 6: disease severity and nonataxia symptoms. *Neurology* 2008;71(13):982–989.
- Muller B, Ilg W, Giese MA, Ludolph N. Validation of enhanced kinect sensor based motion capturing for gait assessment. *PLoS One* 2017;12(4):e0175813.
- Schniepp R, Wuehr M, Neuhaeuser M, et al. Locomotion speed determines gait variability in cerebellar ataxia and vestibular failure. *Mov Disord* 2012;27(1):125–131.
- Ilg W, Fleszar Z, Schatton C, et al. Individual changes in preclinical spinocerebellar ataxia identified via increased motor complexity. *Mov Disord* 2016;31(12):1891–1900.
- Winter DA. *Biomechanics and Motor Control of Human Gait: Normal, Elderly and Pathological*. 2nd ed. Waterloo, Canada: Wiley-Interscience Publication; 1991.
- Cliff N. Answering ordinal questions with ordinal data using ordinal statistics. *Multivar Behav Res* 1996;31(3):331–350.
- Kerby DS. The simple difference formula: an approach to teaching nonparametric correlation. *Compr. Psychiatry* 2014;3:11.IT.13.11.
- Tezenas du Montcel S, Durr A, Rakowicz M, et al. Prediction of the age at onset in spinocerebellar ataxia type 1, 2, 3 and 6. *J Med Genet* 2014;51(7):479–486.
- Faul F, Erdfelder E, Buchner A, Lang AG. Statistical power analyses using G*power 3.1: tests for correlation and regression analyses. *Behav Res Methods* 2009;41(4):1149–1160.
- Globas C, du Montcel ST, Baliko L, et al. Early symptoms in spinocerebellar ataxia type 1, 2, 3, and 6. *Mov Disord* 2008;23(15):2232–2238.

29. Ilg W, Branscheidt M, Butala A, et al. Consensus paper: neurophysiological assessments of ataxias in daily practice. *Cerebellum* 2018; 17(5):628–653.
30. Klockgether T, Mariotti C, Paulson HL. Spinocerebellar ataxia. *Nat Rev Dis Primers* 2019;5(1):24.
31. Buckley E, Mazza C, McNeill A. A systematic review of the gait characteristics associated with cerebellar ataxia. *Gait Posture* 2018; 60:154–163.
32. Ilg W, Timmann D. Gait ataxia-specific cerebellar influences and their rehabilitation. *Mov Disord* 2013;28(11):1566–1575.
33. Jacobi H, du Montcel ST, Bauer P, et al. Long-term disease progression in spinocerebellar ataxia types 1, 2, 3, and 6: a longitudinal cohort study. *Lancet Neurol* 2015;14(11):1101–1108.
34. Diallo A, Jacobi H, Tezenas du Montcel S, Klockgether T. Natural history of most common spinocerebellar ataxia: a systematic review and meta-analysis. *J Neurol* 2021;268(8):2749–2756.
35. Manta C, Patrick-Lake B, Goldsack JC. Digital measures that matter to patients: a framework to guide the selection and development of digital measures of health. *Digit Biomark* 2020;4(3):69–77.
36. Wilke C, Haas E, Reetz K, et al. Neurofilaments as blood biomarkers at the preataxic and ataxic stage of spinocerebellar ataxia type 3: a cross-species analysis in humans and mice. *medRxiv* 2020; 12(7):e11803. <https://doi.org/10.15252/emmm.201911803>
37. Faber J, Schaprian T, Berkan K, et al. Regional brain and spinal cord volume loss in spinocerebellar ataxia type 3. *Mov Disord* 2021;36(10):2273–2281.
38. Cabaraux P, Agrawal SK, Cai H, et al. Consensus paper: ataxic gait. *Cerebellum* 2022;12. <https://doi.org/10.1007/s12311-022-01373-9>. Online ahead of print.
39. Thierfelder A, Seemann J, John N, et al. Real-life turning movements capture subtle longitudinal and Preataxic changes in cerebellar ataxia. *Mov Disord* 2022;37(5):1047–1058.

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

SGML and CITI Use Only

DO NOT PRINT

Author Roles

1. Research Project: A. Conception, B. Organization, C. Execution;
2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.
W.I.: 1A, 1B, 2A, 3A.
B.M.: 1C, 2C, 3B.
J.F.: 1B, 1C, 3B.
J.v.G.: 1B, 2C, 3B.
H.H.: 1C, 2C, 3B.
I.R.V.: 1C, 2C, 3B.
G.H.: 1C, 2C, 3B.
B.v.d.W.: 1A, 2C, 3B.
T.K.: 1A, 2C, 3B.
L.S.: 1A, 2C, 3B.
M.S.: 1A, 2C, 3A.
Statistical analysis was conducted by W.I.

Financial Disclosures

All authors declare no conflicts of interest concerning the research related to the manuscript. B. Müller, Dr. Faber, Dr. van Gaalen, Dr. Hengel, Dr. Vogt, and G. Hennes report no disclosures. Prof. Schöls received consultancy fees by Vico Therapeutics, unrelated to the submitted work. Prof. Synofzik has received consultancy honoraria by Orphazyme Pharmaceuticals, Janssen Pharmaceuticals, Ionis Pharmaceuticals, and speakers' honoraria by the Movement Disorders Society, unrelated to the submitted work. Dr. Ilg received consultancy honoraria by Ionis Pharmaceuticals, unrelated to the submitted work. Prof. van de Warrenburg receives research support from ZonMw, Hersenstichting, Gossweiler Foundation, Radboud University Medical Center, and uniQure; receives royalties from BSL and Springer Nature; and has served on a scientific advisory board of uniQure, all activities outside the submitted work. Prof. Klockgether received personal fees from Roche, UCB, uniQure, and Vico Therapeutics, all activities outside the submitted work.

Relevant Conflicts of Interest/Financial Disclosures

Nothing to report. Full financial disclosures and author roles may be found in the online version of this article.