RESEARCH ARTICLE

Real-Life Turning Movements Capture Subtle Longitudinal and Preataxic Changes in Cerebellar Ataxia

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ABSTRACT: Background: Clinical and regulatory acceptance of upcoming molecular treatments in degenerative ataxias might greatly benefit from ecologically valid endpoints that capture change in ataxia severity in patients' real life.
Objectives: This longitudinal study aimed to unravel quantitative motor biomarkers in degenerative ataxias in real-life turning movements that are sensitive for changes both longitudinally and at the preataxic stage.
Methods: Combined cross-sectional (n = 30) and longitudinal (n = 14, 1-year interval) observational study in degenerative cerebellar disease (including eight preataxic mutation carriers) compared to 23 healthy controls. Turning movements were assessed by three body-worn inertial sensors in three conditions: (1) instructed laboratory assessment, (2) supervised free walking, and (3) unsupervised real-life movements.
Results: Measures that quantified dynamic balance during turning—lateral velocity change (LVC) and outward acceleration—but not general turning measures such as speed, allowed differentiating ataxic against healthy subjects in real life (effect size $\delta = 0.68$), with LVC also differentiating preataxic against healthy subjects ($\delta = 0.53$). LVC was highly correlated with clinical ataxia severity (scale for the assessment and rating of ataxia [SARA] score, effect size $\rho = 0.79$) and patient reported balance confidence (activity-specific balance confidence scale [ABC] score, $\rho = 0.66$). Moreover, LVC in real life—but not general turning measures or the SARA score—allowed detecting significant longitudinal change in 1-year follow-up with high effect size ($r_{prb} = 0.66$).
Conclusions: Measures of turning allow capturing specific changes of dynamic balance in degenerative ataxia in real life, with high sensitivity to longitudinal differences

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in ataxia severity and to the preataxic stage. They thus present promising ecologically valid motor biomarkers, even in the highly treatment-relevant early stages of degenerative cerebellar disease. © 2022 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society

Key Words: turning; cerebellar ataxia; wearable sensors; real-life walking; motor biomarker

Introduction

While manifold targeted molecular treatments for degenerative cerebellar diseases (DCDs) are on the horizon,[1,2] clinical and regulatory acceptance will depend on their proven effects on subject's ataxia in real life. This highlights the need for quantitative ataxia biomarkers remotely monitored during subjects' real life. These quantitative motor biomarkers should be sensitive to longitudinal change as well as to the early—possibly even preataxic—stages of ataxia disease, where molecular treatments are likely most effective.[3]

Recent work focusing on the analysis of straight walking sequences has raised the possibility to capture motor changes in DCDs by remote sensor-based monitoring during daily life.[4] However, although measures of straight walking showed high sensitivity to cross-sectional ataxia severity,[4] other components of real-life walking behavior, like turning, might place higher coordinative demands and, thus, show a higher sensitivity to individual progression, in particular, for preataxic and early disease stages. This hypothesis receives support from a previous study showing that a coordinatively highly demanding task—tandem walking on a foam surface—revealed changes at the preataxic stage of DCD.[5] Turning movements represent a highly relevant component of everyday walking behavior, because 35% to 45% of steps occur within turns.[6] Compared to straight walking, turning movements are suggested to be more challenging in terms of dynamic balance,[7-9] because they involve a stronger demand of anticipatory postural adjustments[10] and trunk-limb coordination strategies.[11]

Existing work in Parkinson's disease,[12-15] multiple sclerosis,[16] cerebellar ataxia,[17,18] and aging[19] focused on the assessment of general turning parameters like turn angle, mean velocity, or the number of steps within the turn. However, these measures do not reflect specific dysfunctional mechanisms like dynamic balance control. Such changes might be more sensitively captured by measures reflecting motor control mechanisms specifically impaired in cerebellar ataxias.

Based on these notions, we hypothesized that dynamic balance measures of turning might be particularly sensitive to subtle ataxia changes not only under supervised task-based conditions, but also during unsupervised, task-free real life both (1) longitudinally and (2) at preataxic and early stages of ataxia disease.

Methods

Participants

Thirty subjects at an ataxic or preataxic stage of DCD (age: 51 ± 15 years) were recruited from the Ataxia Clinics of the University Hospitals Tübingen and Essen. A total of 22 subjects were at the ataxic stage of DCD as defined by a scale for the assessment and rating of ataxia (SARA) score of ≥3 (group ATX; mean SARA score of 9.4 points), and 8 subjects with repeat-expansions in SCA2, SCA3, or SCA6 were at the preataxic stage of DCD (SARA score <3) (group PRE; mean SARA score of 1.37 points).[20] For details of patient characteristics, see the Supplementary Appendix. No individual age is provided for the preataxic subjects, because this would facilitate an individual identification of mutation carriers. DCD subjects were included based on following criteria: (1) manifest or repeat expansion for DCD in the absence of any signs of secondary or other CNS disease; (2) age between 18 and 75 years; and (3) ability to walk without walking aids. Exclusion criteria included cognitive impairment, predominant non-ataxia movement disorders, or orthopedic constraints. None of the patients were receiving symptomatic drug treatment for non-ataxic movement disorder components such as Parkinsonism.

Seventeen of the 30 DCD subjects carried a repeat expansion in SCA1, 2, or 3 (SCA1/2/3 subgroup). We performed all main analyses also in this subgroup, because these fast progressing SCA types are most relevant for upcoming interventions trials.[1,2] Severity of ataxia was rated using the SARA score,[20] which includes three items rating gait and posture (subscore $SARA_{posture\&gait}$),[5,21] one for speech disturbances, and four for limb-kinetic functions. Neurological signs other than ataxia were assessed by the Inventory of Non-Ataxia Signs (INAS).[22]

In addition, we recruited 23 healthy controls (HC: age = 48 ± 15 years). HC subjects had no history of any neurological or psychiatric disease, and did not show any neurological signs on clinical examination. Subjects were analyzed cross-sectionally at baseline and, where available, longitudinally at 1-year follow-up.

This study has been approved by the institutional review board (IRB) of the University of Tübingen (598/2011BO1, 303/2008BO2), including full information of all subjects about respect of autonomy, confidentiality, and fully voluntary participation in the study.

Turning Conditions

Turning movements were recorded in two supervised conditions and one unsupervised condition in real life as the main target condition.

1. Instructed task-based turning (ITT) within a constrained turning task: Subjects were instructed to walk along a parkour at the T-junction of a lab corridor performing 90° and 180° turns as illustrated in Figure 1C and supervised by a study assessor. This task was conducted twice in each direction (1–2 minutes).
2. Supervised free turning (SFT): Turning movements were extracted from unconstrained walking in public indoor and outdoor spaces on a hospital compound (~5 minutes). Subjects were instructed to walk at their preferred speed together with a study assessor, who provided direction during the walking trial. The walking route was crowded to varying degree by other passengers, therefore, partly mimicking real-life settings, but still under supervision and guidance.
3. Real-life turning (RLT): Turning movements were extracted from unconstrained walking during subjects' everyday living without any supervision (total recording time per subject: 4–6 hours). Subjects have to wear the sensors inside and outside their house and to include a minimum half-hour walk. Because the APDM Mobility Lab software is not yet optimized for whole day recordings, subjects were instructed to wear the sensors in consecutive recording sessions, each with a duration of 1 to maximal 2 hours.

To capture the impact of disease on subjective confidence in daily living, DCD subjects were asked to self-report their balance confidence using the activity-specific balance confidence scale (ABC)[23] and two specific questions about turning movements (see the Supplementary Appendix).

Methods for Measuring Turning Movements

Three Opal inertial sensors (APDM, Portland, OR) were attached to both feet and to the posterior trunk at the level of L5 with elastic Velcro bands. Inertial sensor data were wirelessly streamed to a laptop for generation of gait metrics by the APDM Mobility Lab software. For unconstrained walking (SFT, RLT), data

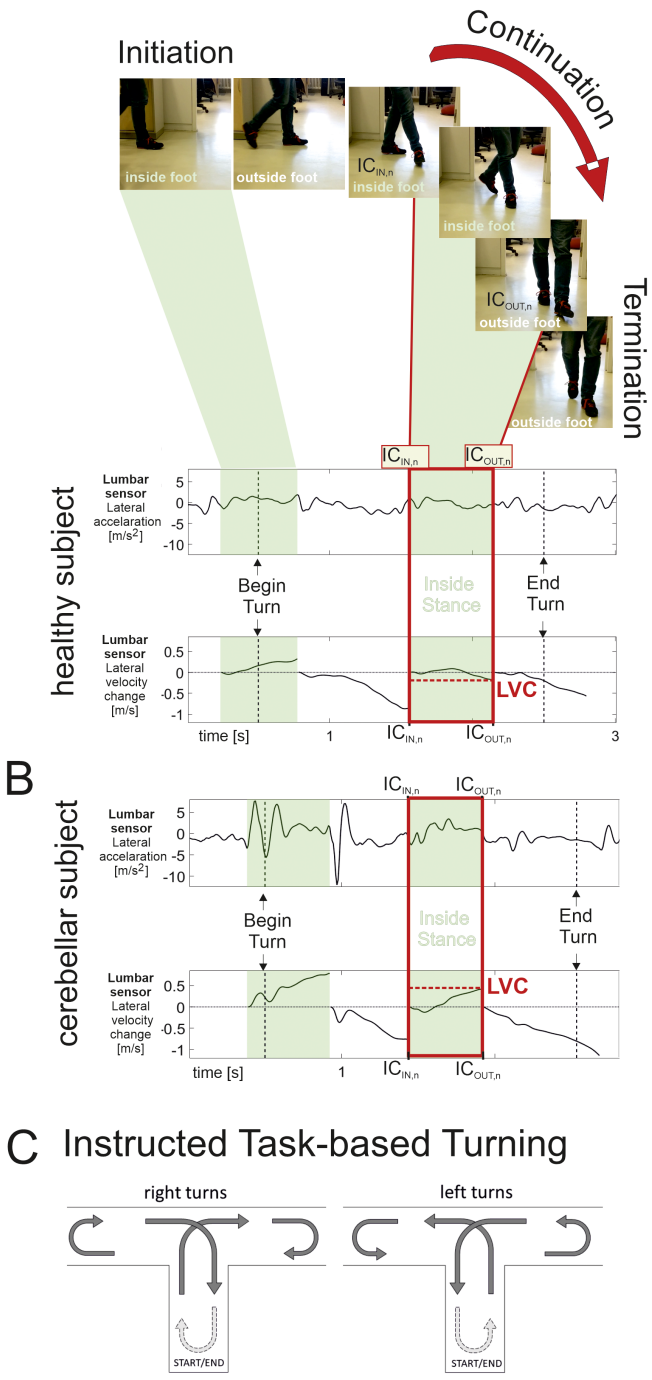

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FIG. 1. Illustration of the lateral velocity change (LVC) turning measure and the instructed task-based turning walkway. (**A**) Computation of the LVC turning measure. Shown are snapshots of the steps of an exemplary 90° turn of a healthy subject and the corresponding trajectories of lateral acceleration and LVC of the lumbar sensor. The LVC measure is determined in inside stance phases (highlighted in green) during the continuation phase (highlighted by red boxes) of the turning movement. This phase lasts from the initial contact (IC) of the inside stance leg (IN) until the next initial contact of the outside (OUT) stance leg. The LVC measure is calculated by integrating the lateral acceleration in the described phase. (**B**) Corresponding diagrams of lateral acceleration and the LVC measure for a 90° turn of a cerebellar patient with moderate ataxia (SARA =10). (**C**) Schematic illustration of the T-junction walkway on a real corridor for the instructed task-based turning (ITT) performing 90° and 180° turns. This procedure was generally conducted twice in each direction, resulting in eight 90° turns (four left and right turns, respectively), and ten 180° turns for each subject.

were logged on each Opal sensor and downloaded after the session. Turns were identified by Mobility Lab using the low-pass filtered angular velocity reoriented to the global reference frame and locating peaks in the rotation around the vertical axis that exceeded 15°/s. The boundaries of each turn were set to the points where the angular velocity crossed 5°/s.[14] Only turns with a duration between 0.5 seconds and 10 seconds and an overall angle above 45° were considered, and turns in the same direction with <50 milliseconds interval were combined into one turn.[14] For each detected turn, we used the following features extracted via the Mobility Lab algorithms: turn angle, duration, velocity, steps within turn, and raw accelerometer data.[14,24] For determining the lateral acceleration, the sensor data was reoriented from the sensor body frame into a global reference frame using the orientation estimates provided by Mobility Lab.[14] This global reference frame was used to align the lateral axis of the lumbar acceleration orthogonal with respect to gravity. Because the Mobility Lab software does not provide step events within extracted turns, step events within turns were determined by a custom algorithm based on continuous wavelet transform.[25]

Because we observed very few 180° U-turns in the unconstrained conditions, we did not include 180° turns in the main analysis (for results of the 180° U-turns in ITT, see the Supplementary Appendix). For the ITT condition, we analyzed 90° turning movements; for the unconstrained conditions SFT and RLT, we included turns between 50° and 120°. In SFT and RLT, turns were only included if two regular steps before and after the turn were detected.

Measures of Dynamic Balance in Turning Movements

In addition to general turning parameters, we focused on measures that allow quantifying impaired dynamic balance control while turning, in particular lateral sway pattern. This was operationalized by the lateral acceleration of the lumbar sensor. Previous work on wearable sensors has shown that such lateral acceleration is correlated to a dynamic stability criterion (margin of stability)[26] during walking and turning.[27] This dynamic stability criterion was defined in the mediolateral dimension by regarding the lateral acceleration $acc_{\mathrm{lat}}^{\mathrm{COM}}$ of the CoM (center of mass) orthogonal to gravity and the direction of travel. Therefore, the change in the lateral velocity $v_{\mathrm{lat}}^{\mathrm{COM}}$ of the CoM during step n is given by,

$$\Delta v_{\mathrm{lat}}^{\mathrm{COM}} = v_{\mathrm{lat}_{n+1}}^{\mathrm{COM}} - v_{\mathrm{lat}_n}^{\mathrm{COM}} = \int_n^{n+1} acc_{\mathrm{lat}}^{\mathrm{COM}}(t)\,dt, \quad (1)$$

whereby $\Delta v_{\mathrm{lat}}^{\mathrm{COM}}$ can be used to determine dynamic stability with respect to foot placement or to describe the amount of corrective foot placement needed to regain stability after a disturbance.[26]

Turning movements can be categorized in three phases: initiation, continuation, termination (eg, Fig. 1A and Supplementary Appendix).[28] Because the largest whole-body angular momentums occur during the continuation phase,[29] our analysis focused on the lateral acceleration during steps within the continuation phase, starting with the initial contact of the inside foot (IC_{IN}) until the subsequent initial contact of the outside foot (IC_{OUT}) (Fig. 1A,B).

The lateral velocity change (LVC) of this period was computed by integrating the lateral acceleration (acc_{lat}) of the lumbar sensor for step n and turn T (Eq. 2).

$$LVC_n^T = \int_{IC_{IN_n}}^{IC_{OUT_n}} acc_{lat}(\mathrm{t})\,dt \quad (2)$$

The LVC^T for turn T was determined by averaging the ${LVC_n}^T$ over all steps n within the turn. Note that for 90° turns, there is often only one step that contributes to the LVC^T of that specific turn T[29] (Fig. 1A,B) and that pure spin turns[18] (see the Supplementary Appendix) are automatically discarded in the LVC computation because such turns contain only one step into and one out of the turn, but none completely within the turn boundaries.

The resulting LVC over all turns for one subject in a condition was determined as the median of all LVC^T of corresponding turns. The LVC describes the relation between acceleration to the inside and outside of the turn curvature. To generalize across turns, we defined outward acceleration to be positive and inward acceleration to be negative. Positive LVC, therefore, denote more velocity toward the outside of the turn curvature, whereas negative LVC indicate more inward velocity.

As complementary measures, we also determined the amount of outward and inward acceleration separately:

$$Outward_{acc_n} = \int_{\mathrm{IC}_{\mathrm{IN}_n}}^{\mathrm{IC}_{\mathrm{OUT}_n}} acc_{\mathrm{lat}}^{\mathrm{out}}(t)\,dt \quad (3)$$

and

$$Inward_{acc_n} = \int_{\mathrm{IC}_{\mathrm{IN}_n}}^{\mathrm{IC}_{\mathrm{OUT}_n}} acc_{\mathrm{lat}}^{\mathrm{in}}(t)\,dt \quad (4)$$

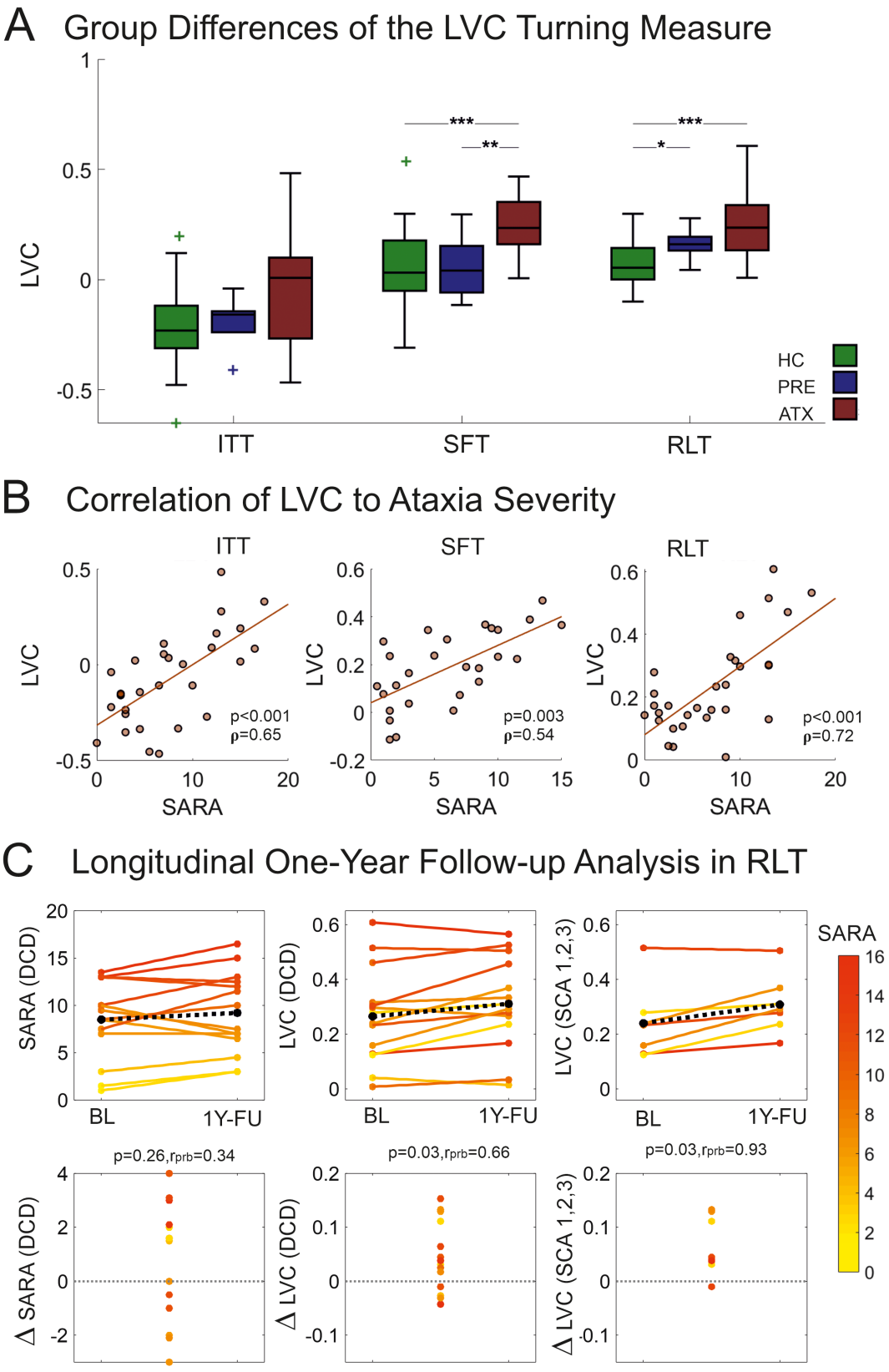
Statistics

Between-group differences were determined by the nonparametric Kruskal-Wallis test. When the Kruskal-Wallis

TABLE 1 *Cross-sectional analysis of turning measures*

		Descriptive statistics			Statistical test results						
		HC	PRE	ATX	KW	HC vs. PRE		HC vs. ATX		PRE vs. ATX	
Measure	**Cond.**	**μ ± σ**	**μ ± σ**	**μ ± σ**	***P***	***P***	**Δ**	***P***	**δ**	***P***	**δ**
Mean velocity	ITT	53.59 ± 13.19	50.48 ± 8.77	50.89 ± 10.07	0.849	0.936	0.03	0.573	0.1	0.816	0.07
	SFT	45.81 ± 8.9	45.76 ± 5.58	47.8 ± 9.25	0.663	0.948	0.02	0.442	0.14	0.465	0.18
	RLT	46.68 ± 6.28	45.24 ± 3.76	47.98 ± 7.37	0.829	0.604	0.13	0.742	0.06	0.656	0.11
Duration	ITT	1.66 ± 0.3	1.71 ± 0.36	1.61 ± 0.33	0.821	0.851	0.06	0.523	0.11	1.00	0.01
	SFT	1.66 ± 0.34	1.59 ± 0.13	1.54 ± 0.31	0.729	0.528	0.15	0.521	0.12	0.724	0.09
	RLT	1.67 ± 0.26	1.67 ± 0.13	1.58 ± 0.3	0.566	0.718	0.09	0.286	0.19	0.76	0.08
Angle	ITT	84.63 ± 9.03	84.44 ± 5.63	80.09 ± 7.75	0.133	0.767	0.09	0.063	0.32	0.223	0.33
	SFT	74.03 ± 11.72	73.2 ± 7.92	69.35 ± 9.09	0.277	0.744	0.08	0.134	0.27	0.311	0.24
	RLT	73.61 ± 5.46	73.17 ± 3.47	70.01 ± 5.09	0.065	0.701	0.1	0.024⋆	0.4	0.197	0.32
No. steps	ITT	3.48 ± 0.68	4.08 ± 1.02	3.35 ± 0.79	0.365	0.194	0.34	0.849	0.03	0.191	0.33
	SFT	3.39 ± 1.22	2.89 ± 0.74	2.83 ± 0.88	0.207	0.274	0.25	0.097	0.29	0.73	0.08
	RLT	3.04 ± 0.82	3.0 ± 0.53	2.7 ± 0.77	0.29	0.884	0.04	0.167	0.23	0.236	0.27
LVC	ITT	−0.2 ± 0.19	−0.19 ± 0.12	−0.05 ± 0.25	0.104	0.809	0.07	0.052	0.33	0.169	0.38
	SFT	0.04 ± 0.2	0.06 ± 0.14	0.22 ± 0.31	0.002⋆⋆	0.648	0.11	0.001⋆⋆⋆	0.59	0.013⋆	0.59
	RLT	0.07 ± 0.1	0.16 ± 0.07	0.26 ± 0.17	<0.001⋆⋆⋆	0.029⋆	0.53	<0.001⋆⋆⋆	0.68	0.214	0.31
$Outward_{Acc}$	ITT	31.0 ± 13.5	27.0 ± 7.4	47.2 ± 24.0	0.006⋆⋆	0.319	0.28	0.006⋆⋆	0.47	0.021⋆	0.63
	SFT	46.5 ± 14.4	44.97 ± 12.17	61.8 ± 13.0	0.003⋆⋆	0.948	0.02	0.002⋆⋆	0.59	0.011⋆	0.62
	RLT	44.5 ± 8.7	49.7 ± 8.2	63.9 ± 17.4	<0.001⋆⋆⋆	0.13	0.37	<0.001⋆⋆⋆	0.7	0.037⋆	0.51
$Inward_{Acc}$	ITT	57.84 ± 19.34	52.51 ± 18.07	54.5 ± 21.56	0.541	0.27	0.304	0.489	0.12	0.697	0.11
	SFT	42.87 ± 16.12	35.04 ± 8.81	28.83 ± 9.57	0.008⋆⋆	0.157	0.33	0.003⋆⋆	0.55	0.129	0.37
	RLT	34.3 ± 10.41	28 ± 3.58	29.93 ± 8.56	0.18	0.075	0.435	0.192	0.229	0.725	0.09

Between-group differences of HC, PRE, and ATX for different turning measures in each of the three study conditions: ITT, SFT, and RLT. Stars indicate significant differences between groups (⋆$P < 0.05$, ⋆⋆$P < 0.01$ Bonferroni-corrected, ⋆⋆⋆$P < 0.001$). KW denotes the result of the Kruskal-Wallis test. δ denotes the effect sizes determined by Cliff's delta. HC, healthy controls; PRE, preataxic subjects; ATX, ataxic subjects; ITT, instructed task-based turning; SFT, supervised free turning; RLT, real life turning; LVC, lateral velocity change.



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test yielded a significant effect ($P < 0.05$), post hoc analysis was performed using a Mann-Whitney U test. Effects sizes were determined by Cliff's delta.[30]

Repeated measurements analyses were performed for longitudinal analyses using the non-parametric Friedman test to determine within group differences between assessments. 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. Effect sizes for the repeated measurements analyses were determined by matched-pairs rank biserial correlation.[31]

We report three significance levels: (1) uncorrected $^{*}P < 0.05$, (2) Bonferroni-corrected for multiple comparisons $^{**}P < 0.05/n$ with n = 3: number of analyzed turning features of dynamic balance, and (3) $^{***}P < 0.001$. Spearman's ρ was used to examine the correlation between turning measures, SARA and ABC scores. Effect sizes ρ were classified as ρ: 0.1 small effect, 0.3 medium effect, 0.5 large effect, and 0.7 very large effect.[32] The test–retest reliability of the LVC measure from independent successive recording sessions in real life was calculated using ICC[2, k][33] (see the Supplementary Appendix for details). Statistical analysis was performed using MATLAB (Version R2018B) (The MathWorks, Natick, MA). Based on the longitudinal changes of the LVC, a sample size estimation was performed using G*power 3.1[34] to determine the required cohort size for detecting a 50% reduction of progression by a hypothetical intervention.

Results

Group Differences Between HC, ATX, and PRE for Specific but Not General Turning Measures

We analyzed 16.8 ± 6.71 turns in the SFT and 78 ± 18 turns in the RLT condition per participant, with no difference between groups (Kruskal-Wallis-test: SFT, $P = 0.32$; RLT, $P = 0.19$). General turning measures did not reveal any group difference (Table 1). In contrast, LVC and $\text{Outward}_{\text{Acc}}$ revealed group differences for all turning conditions. Post hoc analysis revealed group difference between ATX and HC ($P < 0.006$) (Fig. 2A, Table 1), with highest effect sizes ($\delta > 0.68$) in the RLT condition for both LVC and $\text{Outward}_{\text{Acc}}$. Moreover, the LVC revealed differences between PRE and HC for the RLT condition ($P = 0.029$, $\delta = 0.53$) (Table 1). This difference in LVC between PRE and HC was confirmed for the SCA1/2/3 subgroup, also with large effect size ($P = 0.007$, $\delta = 0.82$) (see the Supplementary Appendix). DCD subjects revealed an excellent intraclass correlation (ICC[2, k] = 0.91, CI = [0.8, 0.96]), and specific testing revealed high robustness of our LVC measure against lateral shift of the lumbar sensor (see the Supplementary Appendix).

Sensitivity of Turning Measures to Ataxia Severity: Cross-Sectional Analysis

To analyze sensitivity to ataxia severity, we correlated the turning measures with the SARA score for the ATX group (because the SARA captures clinical ataxia severity only for ataxic, not preataxic subjects).[5,35] Of the general turning measures, mean velocity and number of steps showed correlations only for the SFT condition (Table 2). In contrast, LVC and $\text{Outward}_{\text{Acc}}$ revealed correlations to the SARA score across all turning conditions, with highest effect size ($\rho = 0.79$) for real-life turning (Table 2, Fig. 2B).

In addition, the LVC measure revealed high correlations with patient-reported balance confidence in activities of daily living, assessed by the ABC score ($P < 0.001$, effect size $\rho = 0.66$) (Table 2). In contrast, no significant influence of non-ataxic dysfunctions as determined by the INAS score[36] on turning measures was observed (see the Supplementary Appendix). Moreover, LVC measure did not correlate with severity of pyramidal tract damage/spasticity, as shown by a disease control cohort with pure hereditary spastic paraplegia (HSP) (see the Supplementary Appendix).

Sensitivity of Turning Measures to Longitudinal Change in Real Life

We next analyzed whether the turning measures allow to detect longitudinal changes in real life at 1-year follow-up assessment (duration: 391 ± 69 days). Longitudinal real-life data were available from 14 DCD subjects (12 ATX, 2 PRE) and 13 HCs. Reasons for longitudinal drop-out were unavailability for follow-up assessment ($n = 13$), technical problems in follow-up assessment ($n = 1$), and disability in walking without walking aids at follow-up ($n = 2$).

FIG. 2. Group differences, relation to clinical ataxia severity and change over time for the LVC turning measure. (**A**) Between-group differences of the LVC measure for healthy controls (HC, green), preataxic subjects (PRE, blue) and ataxic subjects (ATX, red) in the different turning conditions: instructed task-based turning (ITT), supervised free turning (SFT) and real life turning (RLT). (**B**) Relationship between SARA score and the LVC measure for the different turning conditions. Shown are all subjects with degenerative cerebellar disease (DCD) including both preataxic and ataxic subjects. (**C**) Within-subject changes between baseline and 1-year follow-up for the total group of subjects with degenerative cerebellar disease (DCD) and for the subgroup SCA1/2/3: (upper panel) Within-subject changes of the SARA score and the measure LVC in the real-life turning condition RLT for the total DCD group and for the SCA1/2/3 subgroup compared at baseline (BL) and 1-year follow-up (1y-FU). (Lower panel) Within-subject changes between baseline and 1-year follow-up represented as delta (Δ). In all panels, SARA scores of individual cerebellar subjects are color coded. Black dotted line = mean change across all subjects. Stars indicate significant differences between groups ($^{*}P < 0.05$, $^{**}P < 0.01$ Bonferroni-corrected, $^{***}P < 0.001$). Effect sizes r_{prb} were determined by matched-pairs rank biserial correlation.

TABLE 2 *Correlations of turning measures with clinical and patient-oriented scores*

		SARA		$SARA_{p\&g}$		ABC score		Question 90° turns		Question 180° turns	
Turning measure	**Condition**	***P***	**ρ**	***P***	**ρ**	***P***	**ρ**	***P***	**ρ**	***P***	**ρ**
LVC	ITT	<0.001***	0.691	<0.001***	0.727	<0.001***	−0.51	0.002**	−0.46	0.016*	−0.36
	SFT	0.005**	0.628	0.027*	0.521	0.015*	−0.6	0.002**	−0.72	0.083	−0.45
	RLT	<0.001***	0.789	<0.001***	0.734	<0.001***	0.66	0.026*	0.45	0.058	0.39
$Outward_{Acc}$	ITT	0.003**	0.585	0.002**	0.611	0.018*	−0.36	0.024*	−0.34	0.093	−0.26
	SFT	0.017*	0.554	0.028*	0.518	0.038*	−0.52	0.01*	−0.62	0.154	−0.37
	RLT	<0.001***	0.816	<0.001***	0.747	0.009**	0.52	0.094	0.35	0.206	0.27
$Inward_{Acc}$	ITT	0.083	0.361	0.081	0.363	0.031*	0.33	0.09	0.26	0.159	0.22
	SFT	0.199	0.317	0.164	0.342	0.039*	0.52	0.001***	0.78	0.06	0.48
	RLT	0.127	0.336	0.212	0.277	0.109	0.34	0.204	0.27	0.11	0.33
Mean velocity	ITT	0.238	0.25	0.252	0.243	0.89	−0.02	0.888	0.022	0.893	0.021
	SFT	0.001**	0.699	0.001**	0.732	0.352	−0.25	0.09	−0.44	0.589	−0.15
	RLT	0.622	0.111	0.332	0.217	0.733	0.074	0.517	0.14	0.325	0.21
Duration	ITT	0.567	0.123	0.343	0.202	0.808	0.039	0.834	−0.03	0.916	0.017
	SFT	0.317	0.25	0.096	0.405	0.003**	0.68	0.024*	0.56	0.002**	0.72
	RLT	0.49	0.155	0.284	0.239	0.38	0.19	0.754	0.068	0.211	0.26
Angle	ITT	0.088	0.356	0.17	0.289	0.379	0.14	0.269	0.17	0.335	0.15
	SFT	0.089	0.412	0.224	0.301	0.05	0.5	0.181	0.35	0.006**	0.66
	RLT	0.131	0.332	0.422	0.18	0.627	0.1	0.348	0.2	0.537	0.13
No. steps	ITT	0.665	0.093	0.768	0.064	0.176	0.21	0.273	0.17	0.354	0.14
	SFT	0.014*	0.57	0.005**	0.635	0.068	0.47	0.002**	0.71	0.133	0.39
	RLT	0.713	0.083	0.878	0.035	0.771	0.063	0.585	0.12	0.381	0.19

Correlations between turning measures and clinical ataxia severity (SARA[20] total score and $SARA_{p\&g}$ posture&gait subscore[21]) as well as subjects' self-reported subjective confidence ratings of balance in everyday activities (ABC score).[24] In addition to the validated questions of the ABC score, we asked the patients two specific questions about their balance confidence in everyday life turning movements of 90° and 180° (see the Supplementary Appendix). Correlations were determined for the cohort of ATX subjects in the three study conditions: ITT, SFT, and RLT. (*$P < 0.05$, **$P < 0.01$ Bonferroni-corrected, ***$P < 0.001$). Effect sizes of correlations are given using Spearman's ρ. ATX, ataxic subjects; ITT, instructed task-based turning; SFT, supervised free turning; RLT, real-life turning, LVC, lateral velocity change

TABLE 3 *Longitudinal analysis of turning measures*

			Descriptive statistics		Statistical testing	
Assessment type	**Measure**	**Group**	**Baseline**	**Follow-up**	***P***	r_{prb}
Clinical measures	SARA	DCD	8.5 ± 4.2	9.2 ± 4.3	0.26	0.34
	$SARA_{p\&g}$	DCD	3.1 ± 2.1	3.3 ± 1.9	0.438	0.35
Turning measures in real life	Angle	DCD	70 ± 6.1	69 ± 3.2	0.855	0.07
		HC	72 ± 5.7	73 ± 8	0.946	0.03
	Mean velocity	DCD	49 ± 8.5	49 ± 8.4	0.67	0.14
		HC	45 ± 6.6	44 ± 8	0.34	0.32
	No. steps	DCD	2.6 ± 0.74	2.7 ± 0.72	1.00	0.1
		HC	3.1 ± 0.95	3.2 ± 0.69	0.883	0.04
	Duration	DCD	1.5 ± 0.33	1.5 ± 0.31	0.625	0.16
		HC	1.7 ± 0.29	1.7 ± 0.32	0.508	0.22
	LVC	DCD	0.27 ± 0.17	0.31 ± 0.17	0.03★	0.66
		HC	0.059 ± 0.1	0.047 ± 0.14	0.588	0.19
	$Outward_{Acc}$	DCD	66 ± 17	69 ± 16	0.463	0.24
		HC	45 ± 7.3	45 ± 10	0.542	0.21
	$Inward_{Acc}$	DCD	33 ± 8.4	28 ± 8.7	0.049★	0.6
		HC	37 ± 12	38 ± 16	0.588	0.19

Longitudinal within-subject comparison of clinical ataxia ratings (SARA[20] total score and $SARA_{p\&g}$ posture&gait subscore[21]) as well as turning measures in real life for baseline and 1-year-follow-up (*P*-values determined by Wilcoxon signed-rank test; effect sizes r_{prb} determined by matched-pairs rank-biserial correlation[32]). Shown are analyses for HC and the group of DCD, consisting of preataxic and ataxic subjects. Stars indicate significant differences between groups (★$P < 0.05$, ★★$P < 0.016$ Bonferroni-corrected, ★★★$P < 0.001$). HC, healthy controls; DCD, degenerative cerebellar disease; LVC, lateral velocity change.

While the SARA score (baseline mean: 8.5, follow-up mean: 9.2, $P = 0.26$, effect size $r_{prb} = 0.34$) and general turning measures failed to detect longitudinal changes (Table 3), paired statistics revealed differences between baseline and follow-up for LVC ($P = 0.03$, $r_{prb} = 0.66$) (Table 3, Fig. 2C). The longitudinal increase of the LVC measure indicates a more pronounced acceleration in the outward direction of around 21% of the difference between HC and DCD at baseline. Sample size estimation shows a required cohort size of n = 66 for detecting a 50% reduction of natural progression by a hypothetical intervention (80% power and 1-sided 5% type I error). Analysis of the SCA1/2/3 subgroup revealed an even larger effect for the LVC measure ($P = 0.03$, $r_{prb} = 0.93$; SARA change for SCA1/2/3: $P = 0.31$, $r_{prb} = 0.46$) (Fig. 2C), resulting in a smaller required cohort size of $n = 34$.

In contrast, there were no longitudinal changes in the LVC for the HC group ($P > 0.5$).

Discussion

We aimed to identify quantitative motor biomarkers for DCDs sensitive to subtle ataxia changes not only under supervised conditions, but also during real life by remote recording via wearable sensors. Because turning movements are particularly challenging for dynamic balance control,[8] we hypothesized that turning measures capturing dynamic balance might be most sensitive for such ataxia-related movement changes. Indeed, LVC in real-life turning movements allowed differentiating not only ataxic subjects, but also preataxic subjects from HCs. In contrast to general turning measures and the SARA score, this specific measure allowed detecting longitudinal changes in 1-year follow-up recordings.

Dynamic Balance as a Sensitive Feature of Ataxic Turning Movements

Compared to other features, the LVC measure delivered the highest effect sizes in ataxic versus healthy subjects in all conditions (Table 1). The specificity of LVC in capturing *ataxia-related* changes in dynamic balance control during turning is supported by the findings that (1) no group differences were observed for ataxic versus control subjects in *general* turning measures; (2) no correlation was found between LVC and general turning

measures (Supplementary Table S2-2); (3) no influence of non-ataxia systems (INAS) on LVC was observed.

This also indicates that the observed differences in LVC are not just secondary to different turning strategies,[11] as these would result in a change of general turning measures. Thus far, ataxic turning has been characterized by an enlarged base of support, shortened step length, and increased number of steps.[18] Most likely, these changes mainly reflect compensatory strategies aiming at reducing the instability arising within turns.[18] Such compensation-induced changes for avoiding instabilities are probably more pronounced in stages of more advanced ataxia. Therefore, they likely are less relevant in early stages of DCD.

Comparing our balance-related turning measures across different turning conditions, we observed high correlations between the constrained lab-based (ITT) and the unconstrained task-free conditions (SFT, RLT), in particular for LVC ($P < 0.001$, $\rho > 0.64$) (see the Supplementary Appendix). This is notable because of two aspects: First, turning behavior during unconstrained walking is more variable compared to standardized assessments. Second, we considered turning movements in the range between 50° and 120° for the free walking conditions, because these naturally occur with highest frequency, whereas only 90° turns were analyzed in the standardized task-based assessment. The correlations between conditions suggest that our turning measure validly captures characteristics of real-life turning behavior, because it is validated by standardized and supervised turns. Moreover, they indicate that also standardized assessments can be exploited to deliver first surrogate snapshots of patients' unconstrained turning performance. However, this comes at a cost of less ecological validity and smaller effect sizes; effect sizes in group differences and correlations were highest in the unconstrained real-life condition (Tables 1 and 2), probably because of the larger amount of turns in this condition.

Measures of Ataxic Turning During Real Life Are Sensitive to Clinical Ataxia Severity and Correlate with Patient-Reported Balance Confidence in Cross-Sectional Analyses

LVC and $\text{Outward}_{\text{acc}}$ were highly correlated to clinical ataxia severity in all conditions, with highest effect sizes in real life (Table 2, Fig. 2B). In addition, our measures reflecting dynamic balance correlated with subjects' self-reported confidence in daily balance activities, as quantified by the ABC score (Table 2). Taken together, this close correlation with both a clinician-reported outcome (SARA) and a patient-reported outcome (ABC) indicate the validity of our measure as a real-life digital motor biomarker for clinical trials: it demonstrates that our measures represent a close surrogate for outcomes that are meaningful to patients, as required by the US Food and Drug Administration for regulatory qualification.[37] It is also consistent with a study of multiple sclerosis that identified turning as an important marker of balance confidence and walking limitations.[38]

Measures of Ataxic Turning During Real Life Are Sensitive to the Preataxic Stage

In addition to the differentiation of ataxic patients from HCs, our results are the first to show a group difference between preataxic subjects and healthy controls in real life walking behavior. The preataxic stage of SCAs attracts increasing research interest because it provides a promising window for early therapeutic intervention before substantial irreversible neurodegeneration has occurred.[1,3]

The observation of preataxic changes in turning movements (Table 1) supports the hypothesis that turning is more challenging in terms of dynamic balance. This is consistent with our earlier study on preataxic subjects that identified changes in a coordinatively more demanding walking task, tandem walk on a mattress, but not in straight walking.[5]

However, there is some inconsistency in the literature, with other studies having reported preataxic changes in straight walking during clinical gait assessments.[39,40] This discrepancy might, most likely, be explained with early clinical gait signs already present in these study cohorts.[39,40] In contrast, none of the preataxic subjects in our cohort showed any clinical gait or balance sign, as indicated by a $\text{SARA}_{\text{posture\&gait}} = 0$ for all preataxic subjects (see the Supplementary Appendix).

Measures of Ataxic Turning Are Sensitive to Longitudinal Change in Real Life

To quantify progression and treatment outcome, measures of real-life walking behavior should be able to capture longitudinal changes that correspond to clinically important differences and relevant changes in patient-centered outcome measures.[1,37,41] Longitudinal progression studies in DCDs are still rare and largely limited to clinical and imaging outcome measures.[42-46] In a multi-center longitudinal study, annual SARA progression rates from 0.8 points (SCA6) to 2.11 points (SCA1) per year[44] and have been suggested to be even slower for non-repeat SCAs.[47,48] Only very few studies examined the longitudinal course of gait, observing limited sensitivity to longitudinal changes.[49,50]

In line with previously reported progression rates, we observed an increase of the SARA score of 0.7 at 1-year follow-up, not reaching significance compared to baseline ($P = 0.26$) (Table 3). In contrast, the significant

longitudinal changes observed by the LVC measure support the notion that turning movements and specific measures capturing its balance control component are sensitive to subtle changes. Given that we observed changes with high effect size in a rather small study cohort (follow-up: $n = 14$ subjects) indicates that our measures might be very sensitive not only for longitudinal change, but also for treatment-related change in upcoming intervention trials. Sample size estimation revealed a required cohort size of $n = 66$ for detecting a 50% reduction of natural progression by a hypothetical intervention. This seems to be remarkable as our study cohort also included rather slow progressive DCD types, for example, SCA6[42] and non-repeat SCAs.[47] Indeed, effect sizes were larger for the SCA1/2/3 subgroup, leading to a required cohort size of $n = 34$ subjects for detecting a 50% reduction of natural progression. In comparison, for clinical measures like SARA, earlier studies reported required cohort sizes of $n > 100$.[45]

Conclusions, Limitations, and Outlook

This study unravels measures reflecting dynamic balance control that allow quantifying real-life turning movements with high sensitivity to subtle changes in both (1) preataxic subjects and (2) longitudinal progression in 1-year follow-up. The findings are limited by our study cohort not being sufficiently powered for stratification according to specific ataxia genotypes and for detecting longitudinal change within the preataxic group only. Moreover, although we could not show any influence on non-ataxia symptoms on our movement measures on the group level, non-ataxia symptoms might have an influence on a genotype- or individual level. Therefore, larger multi-centric future studies focusing on real-life behavior with a higher number of preataxic subjects and sufficiently powered for genotype-specific analyses are required to demonstrate the promises of our measures. Moreover, future studies should also examine whole day recordings and their test–retest reliability potentially influenced by sensor shifts over time.

However, our study might have prepared first steps toward developing regulatory approval of digital-motor biomarkers as endpoints for future treatment trials in DCDs, demonstrating (1) their power as ecologically valid biomarkers by capturing motor behavior in real life, (2) their correlation with both clinical ataxia severity and patient-reported balance confidence outcomes, (3) their sensitivity to subtle changes longitudinally and at early disease stages. These early disease stages of DCD will be crucially important for upcoming molecular treatment trials aiming to prevent disease progression.[1,3]

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Data Availability Statement

Data available on request due to privacy/ethical restrictions

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Supporting Data

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