Inter-segmental coordination amplitude and variability differences during gait in patients with Ehlers-Danlos syndrome and healthy adults

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Abstract

Background: There is limited research examining gait and inter-segmental coordination in patients with Ehlers-Danlos syndrome. The objective was to compare lower extremity inter-segmental coordination amplitude and variability during gait between patients with Ehlers-Danlos syndrome and healthy adults.

Methods: This cross-sectional study included participants with Ehlers-Danlos syndrome (n = 13) and healthy adults (n = 14). Gait data were acquired using a motion capture system and force plates. Participants ambulated at self-selected speeds for five trials. Inter-segmental coordination was quantified using continuous relative phase, which examined the dynamic interaction between the thigh-shank and shank-foot paired segments (i.e. phase space relation). A 2-way mixed analysis of variance examined the effects of groups (Ehlers-Danlos and healthy) and gait phases (stance and swing phase) on inter-segmental coordination amplitude and between-trial variability. Effect sizes were calculated using Cohen's *d*.

Findings: The Ehlers-Danlos group had greater inter-segmental coordination variability compared to the healthy group for foot-shank and shank-thigh segment pairs in the sagittal plane over stance and swing phases *(P*=0.04; small to large effect sizes*)*. The Ehlers-Danlos group also had greater variability in the frontal plane at the foot-shank segment pair during stance phase (*P*=0.03; large effect). There were no differences in inter-segmental coordination amplitude between groups (*P*=0.06 to 0.85).

Interpretation: Patients with Ehlers-Danlos syndrome have more variability between gait trials in lower limb motor coordination than healthy adults. This may be related to the impaired proprioception, reduced strength, pain, or slower gait speed seen in this population.

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Keywords: Ehlers-Danlos syndrome; Inter-segmental coordination; gait; kinematic

1. Introduction

Ehlers-Danlos syndrome (EDS) is a group of rare genetic connective tissue disorders affecting one in 10000 people and is characterized by generalized joint hypermobility, skin hyper-elasticity, tissue fragility, and pain (Malfait et al., 2017). Thirteen heterogeneous EDS subtypes exist, with the most common being the hypermobility and classical subtypes (Malfait et al., 2017). Many patients with EDS display muscle weakness, atrophy, and proprioception deficits (Rombaut et al., 2012; Scheper et al., 2017). Research has demonstrated significantly reduced maximal knee strength despite normal muscle mass in patients with EDS, supporting the notion that strength deficits may stem from collagen abnormalities in the muscle extracellular matrix (Rombaut et al., 2012). Patients with EDS have impairments in proprioception including increased sway during standing and walking tasks (Galli et al., 2011b; Rombaut et al., 2011; Scheper et al., 2017), and reduced precision during hand localization (Clayton et al., 2015). Impaired proprioception may occur because of articular laxity, wherein diminished tissue stiffness increases the activation threshold for proprioceptors (Scheper et al., 2017). Altered strength and proprioception may explain some of the gait abnormalities found in these patients.

Studies have examined gait in patients with EDS, with most focusing on the hypermobile EDS subtype. Differences in spatiotemporal parameters have been found, including lower anterior step length and gait speed (Cimolin et al., 2011; Galli et al., 2011a; Robbins et al., 2019; Rombaut et al., 2011) compared to healthy adults. Research on the ankle joint in patients with EDS has revealed reduced peak power (Galli et al., 2011a), as well as abnormal sagittal joint angles in some studies (Cimolin et al., 2011) and normal values in others (Robbins et al., 2019). Results are mixed regarding the knee, with some studies

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showing similar joint angles to healthy adults (Galli et al., 2011a; Robbins et al., 2019) and others revealing abnormalities (Celletti et al., 2013; Cimolin et al., 2011). Muscle activation during gait is altered with some lower extremity muscles displaying either prolonged or delayed activation, and the these changes are most apparent during stance phase (Robbins et al., 2019). Researchers speculate that gait deviations can be attributed to a combination of reduced proprioception, muscle weakness, joint hypermobility, pain, and fear of falling (Celletti et al., 2013; Cimolin et al., 2011; Galli et al., 2011a; Rombaut et al., 2011).

Efficient human gait involves the coordinated and rhythmic movement of joints and requires precise neuromuscular control. Inter-segmental (or inter-joint) coordination explores these dynamic interactions as they occur between paired segments (e.g. shank-thigh) or joints during a movement task and can be quantified using measures such as continuous relative phase (CRP) (Hamill et al., 1999). A certain degree of variability in inter-segmental coordination is important for stable and flexible movement patterns (Hamill et al., 1999). However, the appropriate amount of variability is not uniform across all joint pairs and is altered in certain conditions (e.g. Parkinson's disease) (Chiu and Chou, 2013; Israeli-Korn et al., 2019). When examining knee-ankle inter-joint coordination during gait, Chiu and Chou (2013) found that elderly adults with a recent history of falls had elevated variability during stance phase and lower variability during swing phase when compared to non-fallers. Studies have also found that pain may constrain movement and decrease inter-joint variability (Hamill et al., 1999). For instance, patients with chronic low back pain had lower trunk-pelvis and pelvis-thigh inter-segmental coordination variability during gait compared to healthy adults (Ebrahimi et al., 2017). In contrast, altered gait due to injury or dysfunction may increase coordination variability. Patients with severe knee osteoarthritis demonstrated higher lower extremity inter-segmental coordination variability during gait compared to healthy

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adults, although differences depended on the phase of gait (Wang et al., 2021). A consensus on whether increased or decreased inter-segmental coordination is indicative of pathology or dysfunction has yet to be determined and more research is required.

To our knowledge, no study has examined inter-segmental coordination patterns and variability in patients with EDS. These patients have strength, proprioception, and balance deficits, but it is unclear how these deficits impact lower extremity coordination during gait (Rombaut et al., 2011; Scheper et al., 2017). Furthermore, differences in coordination variability might vary based on the phase of gait, as has been found in other patient populations (Chiu and Chou, 2013; Wang et al., 2021). Investigating these concepts in patients with EDS will further our understanding of how this disease affects movement and motor control. Therefore, the objective was to compare lower extremity inter-segmental coordination amplitude and between-trial variability during gait between patients with EDS and healthy adults. It was hypothesized that the participants with EDS would have increased inter-segmental amplitude and increased between-trial variability during gait because of neuromuscular and proprioceptive deficits. These differences might be more evident during stance phase since there are more demands on the neuromuscular system to control loading.

2. Methods

2.1 Study Design and Participants

This was a secondary analysis of a study previously comparing joint angles and muscle activation during gait between participants with EDS and healthy adults (Robbins et al., 2019). This cross-sectional study recruited participants with EDS from the Lethbridge-Layton-MacKay Rehabilitation Centre in Montreal, Canada. Participants were recruited by convenience sampling between May and July of 2018. Inclusion criteria included participants between 18 to 80 years of age, diagnosis of either EDS hypermobility or classical subtype,

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and the ability to walk a city block. EDS diagnosis was made by a rheumatologist using the Villefranche Nosology criteria (Beighton et al., 1998) or the updated International EDS Consortium criteria (Malfait et al., 2017). The exclusion criteria were: requirement of braces to ambulate, leg trauma or surgery in the past year, current pregnancy, neurological conditions (e.g. previous stroke), or severe cardiorespiratory conditions. The same number of healthy adults were enrolled using advertisements and word of mouth. In addition to the above exclusion criteria, healthy participants were excluded if they had a family history of EDS, history of joint hypermobility disorders, or recurrent joint dislocations. No formal sample size calculation was carried out due to the low prevalence of EDS and all available participants with EDS within our institution were invited to participate. Informed consent was obtained from all participants prior to data collection. This study was approved by the Centre de recherché interdisciplinaire en réadaptation du Montréal métropolitain (Montreal, Canada) research ethics board.

2.2 Group Descriptors

Group descriptors (height, age, sex) were collected. Pain intensity on the day of data collection was measured with a 100-mm visual analogue scale, with higher scores representing greater pain intensity.

2.3 Gait Acquisition

Lower extremity segment angles during gait were collected with an eight-camera, three-dimensional optical motion capture system (OQUS 300+, Qualisys, Göteborg, Sweden), sampled at 100 Hz, and two synchronized force plates (BP400600, Advanced Mechanical Technology Inc., Watertown, USA), sampled at 2000 Hz. Reflective markers (12.7 mm diameter) were attached to bony landmarks per established protocols (Collins et al., 2009) over the following landmarks bilaterally: lateral malleolus, first and fifth metatarsal heads,

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calcaneus, lateral femoral epicondyle, greater trochanter, anterior superior iliac spine, posterior superior iliac spine, and acromial process. Clusters of four markers were placed bilaterally on the mid-shank and mid-thigh regions. Reflective markers were added to the third metatarsal head, medial malleolus, and medial femoral epicondyle for static measurements and were removed before gait trials. Data collection was performed using Qualisys Track Manager (version 2.16, Qualisys, Göteborg, Sweden).

Firstly, static standing trials were obtained once reflective markers were in place. During the static trial, mass measurements and segment definitions were collected as participants were asked to stand on the force plate. The next step aimed to determine hip joint centres by asking participants to execute hip flexion/extension and abduction/adduction in single-leg stance. Finally, participants were asked to walk in a straight line at their normal speed. Each participant was allotted at least two practice trials. Eight gait trials were collected to account for possible errors during data collection. However, only five trials were used for data analysis. Participants wore their own shoes during data collection to favour their comfort and sense of security since many participants with EDS had foot deformities and/or foot orthoses. Participants were also allowed to take breaks if they expressed fatigue.

2.4 Gait Data Processing

Motion capture and force plate data were processed with recursive, low-pass, fourth-order Butterworth filters with cut-off frequencies of 6 Hz and 20 Hz, respectively (Antonsson and Mann, 1985; Winter, 2005). Ankle and knee joint centres were set to halfway between the malleolus and epicondyles markers, respectively (Collins et al., 2009). Functional hip joint centres were calculated using previously described methods (Schwartz and Rozumalski, 2005) and all participants had sufficient hip motion to calculate the hip centres. Gait speed was calculated as the derivative of the posterior superior iliac spine markers in the direction

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of forward progression. Segment angles for the thigh, shank and foot were calculated about the lab coordinate system using an Euler XYZ (sagittal, frontal, transverse) sequence. Force plate data were used to identify gait events including the first initial contact and toe-off. The subsequent initial contact was identified using a kinematic based method (Stanhope et al., 1990). Only the dominant leg was considered for all participants. Data processing was performed using Visual3D (v5, C-motion Inc., Germantown, USA).

2.5 Inter-Segmental Coordination- Continuous Relative Phase (CRP)

Inter-segmental coordination was quantified using CRP. This measures the phase space relation between two segments. In other words, the CRP quantifies the lag between two moving segments and examines whether the segments are moving in-phase (Lamb and Stöckl, 2014). Firstly, segment angles for the thigh, shank, and foot were padded with 100 data points using a double reflection method to prevent end effects that can occur with the CRP calculation (Ippersiel et al., 2019). This data was then amplitude centred around zero using previously described methods (Lamb and Stöckl, 2014). The phase angle for each segment was determined using a Hilbert transform method as previously described (Lamb and Stöckl, 2014). The CRP was determined as the subtraction of the phase angle from the proximal minus the distal segment. CRP values were constrained between 0˚ and 180˚ (Lamb and Stöckl, 2014). The CRP was calculated for the thigh-shank and shank-foot segments in all three planes: sagittal, frontal and transverse. CRP values near 0˚ represent in-phase coupling between segments while values near 180˚ represent out-of-phase coupling. A summary of this process is provided in Supplemental Fig. 1. CRP waveforms were time normalized to 60 data points for stance phase (initial contact to toe-off) and 40 data points for swing phase (toe-off to second initial contact) using cubic spline interpolation.

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CRP amplitude was measured using mean absolute relative phase (MARP), which measures the magnitude of the in-phase/out-of-phase coupling. This was calculated by determining the ensemble CRP curve from the five trials for each participant and then taking the mean of this curve. Higher MARP values represented more out-of-phase coupling. CRP between-trial variability for a participant was determined using deviation phase (DP). For each participant, the standard deviation of CRP waveforms across the five trials for each 1% of the gait cycle was determined to produce a DP waveform and then the mean of this waveform was calculated. Higher DP values represented greater variability. MARP and DP values were determined for stance and swing phase in both segment pairs (thigh-shank, shank-foot) in all three planes. Calculations for CRP were completed using custom scripts in MATLAB (2018a, MathWorks Inc., Natick, USA).

2.6 Statistical and Data Analysis

Descriptive statistics were determined for group descriptors and study variables. Independent t-tests compared group descriptors, pain intensity, and gait speed between EDS and healthy groups. A two-way mixed analysis of variance (ANOVA) was used to measure the effects of groups (between-group; EDS vs healthy) and gait cycle phases (within-group; stance vs swing phase) and their interaction. This analysis was repeated for both the MARP and the DP, in the two different segment pairs (foot-shank, shank-thigh) and for all three planes. The level of significance was set at $\alpha = 0.05$. In the case of significant interactions, Bonferroni corrections were used to adjust for multiple pairwise comparisons. Mean differences with 95% confidence intervals were determined for pairwise comparisons. Cohen's *d* measured effect sizes between groups for each gait phase; $d = 0.20$ represents a small effect size, $d = 0.50$ a medium effect size, and $d = 0.80$ a large effect size (Cohen, 1988). All statistical analyses were performed using SPSS (version 24; IBM, Chicago, IL,

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USA). Microsoft Excel (Microsoft Corporation, Redmond, USA) was also used for effect size calculations.

3. Results

3.1 Study Sample and Descriptive Statistics

Fourteen participants with EDS were enrolled in the study, although one participant could not complete gait testing. This resulted in 13 participants with EDS (11 women, 2 men; 2 classical subtype, 11 hypermobility subtype) available for analysis (Table 1). Fourteen healthy participants (12 women, 2 men) were also recruited (Table 1). A flow diagram showing recruitment and exclusions is provided in Supplemental Fig. 2. Pain intensity was significantly higher in the EDS group ($P<0.001$) (Table 1). Gait speed was significantly higher ($P=0.01$) in the healthy group compared to the EDS group (Table 1). Means and standard deviation MARP and DP values are provided in Table 2.

3.2 Foot-Shank Inter-segmental Coordination

For the foot-shank DP in the sagittal plane, there were statistically significant gait phase ($P<0.001$) and group ($P=0.04$) main effects, but the interaction ($P=0.69$) was not significant (Table 3). The EDS group had higher DP values (i.e. greater between-trial variability for each participant) than the healthy group (Fig. 1). These effect sizes were moderate and large for the stance and swing phases, respectively (Table 4).

In the frontal plane, the foot-shank DP had a statistically significant interaction effect ($P=0.03$), but the gait phase ($P=0.08$) and group ($P=0.11$) main effects were non-significant (Table 3). The EDS group had higher DP values during stance phase ($P=0.005$; Fig. 1) and the effect size was large (Table 4). There were no between-group differences during swing phase (Table 4).

3.3 Shank-Thigh Inter-segmental Coordination

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For the shank-thigh DP in the sagittal plane, there were significant gait phase (P=0.01) and group (P=0.04) main effects, and the interaction (P=0.08) was not significant (Table 3). The EDS group had higher DP values than the healthy group (Fig. 1), representing greater between-trial variability. The effect sizes were large and small for the stance and swing phase, respectively (Table 4).

No additional significant group or interaction effects were revealed, including for all MARP variables (Table 3). Figures of the CRP waveforms are provided in Supplemental Fig. 3-5.

4. Discussion

To our knowledge, this is the only study to examine inter-segmental coordination during gait in patients with EDS. Participants with EDS had higher between-trial, inter-segmental coordination variability in the sagittal plane for both foot-shank and shank-thigh segment pairs during the stance and swing phase of gait, as well as in the frontal plane for the foot-shank during stance. In other words, they had increased coordination variability between gait strides. However, the CRP amplitude (i.e. MARP) was not significantly different between groups. Understanding how coordination is affected during gait and the factors that contribute to these abnormalities will lead to improved functional rehabilitation programs that can target specific neuromuscular impairments.

Our findings indicate that participants with EDS had increased between-trial, sagittal inter-segmental coordination variability in the lower limb when compared to healthy adults. Furthermore, they had increased variability during the stance phase for the foot-shank segment in the frontal plane. Although the exact mechanisms influencing these outcomes are unknown, altered motor function, proprioception, fatigue, pain, or gait speed may play a role (Celletti et al., 2013; Rombaut et al., 2012; Rombaut et al., 2011; Scheper et al., 2017). First,

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muscle force output in patients with EDS is reduced, and muscle activation is delayed and/or prolonged during gait (Galli et al., 2011a; Robbins et al., 2019; Rombaut et al., 2012). This abnormal feedforward activation may contribute to reduced precision (Clayton et al., 2015), as well as inadequate motor corrections and increased movement error. Second, excessive variability may arise from altered proprioceptive feedback previously seen in patients with EDS (Clayton et al., 2015; Galli et al., 2011b; Rombaut et al., 2012; Scheper et al., 2017). Connective tissue defects can impair the mechanical sensitivity of muscle spindles and Golgi tendon organs, which can contribute to delayed or inaccurate feedback regarding both the position of limbs and the length or force of muscle-tendon units throughout the gait cycle. Third, fatigue is a common symptom of EDS. Its severity has been directly linked to muscle weakness (Voermans and Knoop, 2011), and researchers (Celletti et al., 2013) have found that higher fatigue in patients with EDS results in reduced ankle ground reaction force during gait. Finally, pain intensity was higher and gait speed was lower in the EDS group. Both pain and gait speed have been shown to impact gait metrics in other populations (Buddhadev et al., 2020; Henriksen et al., 2010), and thus these factors might account for differences in coordination variability between the EDS and healthy groups. A potential method to account for differences in pain and gait speed would be to include them as covariates in an analysis of covariance (ANCOVA). However, both pain and gait speed are dependent on the group (EDS, healthy), and including them would violate the ANCOVA assumption of independence of the covariate with the independent variable (i.e. group) (Miller and Chapman, 2001). These potential causes of increased coordination variability are speculative and it is likely that a combination of factors contribute to this finding. Additional, research is required to test these hypotheses.

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Although not examined in this study, patients with EDS have been described as more likely to have a history of falls and fear of falling when compared to healthy adults (Rombaut et al., 2011). A previous study found that coordination variability in patients with multiple sclerosis was greater in those with a history of falls when compared to non-fallers (Salehi et al., 2020). It would be beneficial to study if coordination variability is a risk factor for falls in patients with EDS, and whether it is related to the balance dysfunctions previously described (Rombaut et al., 2011). Such deficits are potential targets for treatment. Despite this research gap, this study's exploration of altered inter-segmental coordination during gait has furthered our understanding of motor control mechanisms in patients with EDS. By understanding the specific motor control mechanisms behind these impairments, we hope to be able to target the appropriate neuromuscular mechanisms and improve functional rehabilitation programs for patients with EDS. This could include functional training programs that include strengthening, proprioceptive exercises, and gait retraining. Rehabilitation interventions that address proprioceptive deficits in patients with EDS have been evaluated (Celletti et al., 2011; Dupuy et al., 2017; Peterson et al., 2018), and research is required to determine if such interventions can improve gait outcomes including inter-segmental coordination variability.

Certain study limitations should be considered. The relatively rare prevalence of EDS resulted in a small sample size. To maximize recruitment, the EDS group had a large age range (24 to 62 years). It is unclear how gait changes as patients with EDS age and this might have impacted the findings. The majority of participants had the hypermobility EDS subtype, and results cannot be generalized to other subtypes. Likewise, participants with EDS were higher functioning (i.e. able to ambulate independently) and results cannot be generalized to patients with greater disability. Participants wore their shoes during gait testing, and this might affect some gait metrics. Gait speed and pain intensity were different between groups

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and are potential confounders. Gait speed was not controlled during testing to ensure more natural motor patterns during ambulation. Finally, the experimental critical p value (0.05) was not adjusted to account for Type I error. There were 12 ANOVAs conducted, one for each dependent variable, and a Bonferroni adjustment would have lowered the critical p value to 0.004 (0.05/12). Using this adjusted critical p value, most gait phase main effects remained statistically significant; however, the group main effect and interaction effect would not have been statistically significant ($p>0.004$). The experimental critical p value across all test was not adjusted based on previous recommendations and because it would have increased the Type II error rate (Barnett et al., 2021; Streiner and Norman, 2011).

5. Conclusion

In conclusion, participants with EDS had higher between-trial, inter-segmental coordination variability for the foot-shank and shank-thigh segment pairs when compared to healthy adults. The exact mechanism behind this finding is unknown but is likely related to impairments in muscle strength and proprioception, increased fatigue, pain, or reduced gait speed. Further research is needed to elucidate the mechanisms, and to guide future rehabilitation interventions for patients with EDS.

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Data Statement

Data are not available.

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Table 1
Means (standard deviation) for group descriptors and gait speed for Ehlers-Danlos syndrome (EDS) and healthy groups.

Variables	EDS Group (n = 13, 11 women)	Healthy Group (n = 14, 12 women)	*P-value**
Age (years)	42 (12)	50 (16)	0.17
Height (m)	1.63 (0.09)	1.64 (0.08)	0.16
Mass (kg)	72.8 (21.0)	63.2 (13.2)	0.16
Body mass index (kg/m^2)	25.4 (6.2)	23.5 (4.6)	0.36
Gait speed (m/s)	1.09 (0.26)	1.32 (0.17)	0.01
VAS Pain (/10)	5 (2)	0 (1)	<0.001

**P-value* from independent t-test

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Table 2
Mean (standard deviation) of inter-segmental coordination amplitude (MARP) and variability (DP) for each axis, segment pair and gait phase for EDS and healthy groups.

			EDS		Healthy	
Axis	Segment Pair	Gait Phase	MARP (˚)	DP (˚)	MARP (˚)	DP (˚)
Sagittal	Foot-Shank	Stance	32.49 (5.18)	3.93 (1.55)	29.76 (5.31)	3.18 (0.84)
		Swing	10.52 (3.43)	2.30 (0.60)	8.92 (2.14)	1.74 (0.73)
	Shank-Thigh	Stance	49.01 (10.80)	10.70 (5.64)	48.36 (9.03)	6.73 (3.29)
		Swing	61.65 (5.33)	6.48 (1.78)	57.86 (5.22)	5.75 (2.65)
Frontal	Foot-Shank	Stance	114.59 (31.98)	27.23 (9.39)	115.17 (36.01)	17.23 (7.46)
		Swing	49.77 (19.98)	26.27 (12.34)	52.81 (21.43)	26.19 (8.94)
	Shank-Thigh	Stance	50.63 (28.94)	24.04 (8.73)	48.09 (41.91)	16.53 (8.43)
		Swing	85.61 (33.87)	21.87 (8.13)	82.35 (34.99)	21.66 (8.77)
Transverse	Foot-Shank	Stance	52.36 (26.04)	25.49 (16.71)	61.58 (18.65)	22.83 (14.54)
		Swing	50.53 (28.68)	27.11 (9.95)	51.93 (16.44)	19.58 (10.86)

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	Shank-Thigh	Stance	39.05 (15.19)	20.94 (11.22)	42.41 (22.21)	18.40 (9.52)
		Swing	51.01 (24.04)	21.54 (10.90)	67.60 (27.27)	20.42 (9.24)

Table 3
Summary of two-way mixed analysis of variance results for the inter-segmental coordination amplitude (MARP) and coordination variability (DP).

Axis	Segment Pair		Main Effect		Interaction
			Gait Phase	Group	Gait Phase * Group
			F-test (*P-value*)		
Sagittal	Foot-Shank	MARP	**330.3 (<0.001)**	3.74 (0.06)	0.23 (0.64)
		DP	**39.41 (<0.001)**	**4.87 (0.04)**	0.16 (0.69)
	Shank-Thigh	MARP	**45.46 (<0.001)**	0.74 (0.40)	0.92 (0.35)
		DP	**8.74 (0.01)**	**4.74 (0.04)**	3.41 (0.08)
Frontal	Foot-Shank	MARP	**132.74 (<0.001)**	0.04 (0.85)	0.05 (0.83)
		DP	3.35 (0.08)	2.82 (0.11)	**5.16 (0.03)**
	Shank-Thigh	MARP	**37.51 (<0.001)**	0.05 (0.82)	0.004 (0.95)
		DP	0.54 (0.47)	2.22 (0.15)	3.28 (0.08)

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Transverse	Foot-Shank	MARP	3.82 (0.06)	0.41 (0.53)	1.78 (0.19)
		DP	4.2 (0.05)	0.03 (0.85)	0.96 (0.34)
	Shank-Thigh	MARP	**17.89 (<0.001)**	1.74 (0.20)	2.27 (0.14)
		DP	0.51 (0.48)	0.28 (0.60)	0.15 (0.70)

Significant differences (P<0.05) are in bold.

Table 4
Mean difference (95% confidence interval) and effect sizes of inter-segmental coordination amplitude (MARP) and coordination variability (DP) across the gait phases, axes, and segment pairs.

Axis	Segment Pair	Gait Phase	Mean Difference (95% confidence interval)		Effect Size*	
			MARP (˚)	DP (˚)	MARP	DP
Sagittal	Foot-Shank	Stance	-2.73 (-6.89, 1.44)	-0.75 (-1.73, 0.23)	0.519	0.605
		Swing	-1.60 (-3.85, 0.65)	-0.55 (-1.08, -0.02)	0.565	**0.825**
	Shank-Thigh	Stance	-0.65 (-8.52, 7.22)	-3.97 (-7.60, -0.34)	0.065	**0.868**
		Swing	-3.79 (-7.98, 0.39)	-0.73 (-2.53, 1.07)	0.065	0.321
Frontal	Foot-Shank	Stance	0.58 (-26.50, 27.66)	-10.00 (-16.70, -3.31)	-0.017	**1.185**

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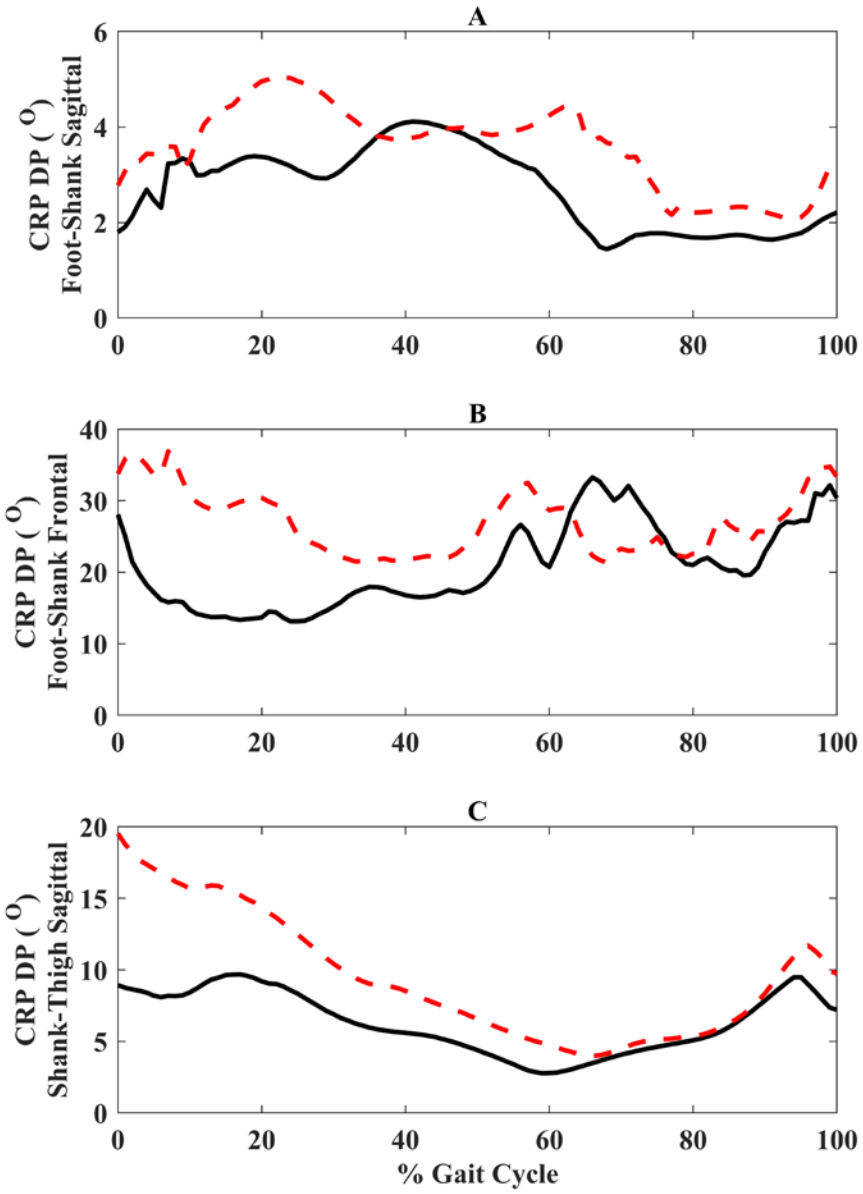
		Swing	3.04 (-13.42, 19.50)	-0.07 (-8.42, 8.56)	-0.146	0.007
	Shank-Thigh	Stance	-2.54 (-31.31, 26.24)	-7.51 (-14.31, -0.71)	0.070	**0.876**
		Swing	-3.26 (-30.59, 24.08)	-0.21 (-6.93, 6.51)	0.070	0.025
Transverse	Foot-Shank	Stance	9.22 (-8.63, 27.07)	1.61 (-9.19, 12.42)	0.410	-0.118
		Swing	1.40 (-16.95, 19.75)	-3.25 (-13.37, 6.87)	-0.410	0.255
	Shank-Thigh	Stance	3.36 (-11.84, 18.57)	-2.54 (-10.76, 5.69)	-0.176	0.244
		Swing	16.59 (-3.86, 37.04)	-1.12 (-9.12, 6.87)	-0.176	0.112

* Effect sizes were determined using Cohen's *d*. Large effect sizes ($d > 0.80$ or $d < -0.80$) are bolded.



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583 Fig. 1. Group ensemble means of the continuous relative phase (CRP) deviation phase (DP)
584 waveforms during gait in the Ehlers-Danlos syndrome (red dashed lines) and healthy (solid black line)
585 groups for the A) foot-shank in the sagittal plane, B) foot-shank in the frontal plane, and C) shank-
586 thigh in the sagittal plane. Figures may appear in greyscale in print editions but are available in color
587 online.
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