Check for updates

Original Article

Gait Analysis in Rett Syndrome: Integrating Linear and Nonlinear Techniques

Journal of Child Neurology
2026, Vol. 41(5) 647-665
© The Author(s) 2025

Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/08830738251371586
journals.sagepub.com/home/jcn
Mary Ann Liebert
A Part of Sage

Dacia Martinez Diaz, BS[1,2], Brock Futrell, MS[1,2], Bernhard Suter, MD[3,4], and Charles S. Layne, PhD[1,2]

Abstract

Rett syndrome is a rare neurodevelopmental disorder that significantly impairs bipedal postural control and walking ability. This study quantifies the gait characteristics of 22 females with Rett syndrome (divided into 3 age groups) and compares them with age-matched neurotypical females. Bilateral sagittal plane joint angles of the hip, knee, and ankle were analyzed. Measures included joint range of motion, stride time, peak angular velocity, angle-angle diagrams, phase portrait areas, and asymmetries. Results revealed reduced joint range of motion and angular velocity in individuals with Rett syndrome, as well as greater asymmetries in gait parameters reflecting disruptions in bilateral coordination. Phase portraits and angle-angle diagrams indicated preserved coordination in proximal joints but greater variability at the ankle. Ankle movement in individuals with Rett syndrome aged 9-14 years showed a closer resemblance to Controls. These findings identify underlying lower limb motion patterns that contribute to gait deficits in Rett syndrome, guiding future targeted interventions to improve their mobility.

Keywords

gait, kinematic analysis, Rett syndrome, neurodevelopmental disorders, Symmetry Index

Received: February 21, 2025; revised: July 16, 2025; accepted: August 7, 2025

Rett syndrome is a rare neurodevelopmental disorder that predominantly affects females, with a pooled prevalence estimate of 7.1 per 100 000 females.[1] The disorder is primarily attributed to variants in the methyl-CpG-binding protein 2 (*MECP2*) gene, with approximately 95% of typical Rett syndrome cases associated with such genetic variants. Initially, affected individuals exhibit seemingly neurotypical developmental trajectories until around 6-18 months of age, after which a period of regression ensues, marked by the loss of motor skills, language acquisition, and social interaction capabilities. This regression phase is followed by a period of stabilization, albeit with persistent impairments in motor function, gait performance, communication, and overall quality of life.[2]

Rett syndrome poses significant challenges to affected individuals and their caregivers because of its profound impact on various aspects of development and functioning. It is characterized by a spectrum of disabling symptoms, including midline stereotypic hand movements, abnormal breathing patterns and bruxism, apraxia, ataxia, muscle tone abnormalities, limb rigidity, scoliosis, and gastrointestinal dysfunction, to mention some of the major ones. Both fine and gross motor skills are significantly impaired, with prominent deficits observed in bipedal postural control and walking ability.[3–5] Despite an initial period of stabilization, walking capacity deteriorates with age, leaving less than half of individuals with Rett syndrome able to walk[6,7] and many of these requiring assistance.[8,9] These mobility limitations likely contribute to reduced physical fitness and overall health status in patients with Rett syndrome.

Several studies have elucidated various gait characteristics exhibited by females with Rett syndrome. These

[1]Department of Health and Human Performance, University of Houston, Houston, TX, USA
[2]Center for Neuromotor and Biomechanics Research, University of Houston, Houston, TX, USA
[3]Blue Bird Circle Rett Center, Texas Children's Hospital, Houston, TX, USA
[4]Deparments of Pediatrics and Neurology, Baylor College of Medicine, Houston, TX, USA

Corresponding Author:
Bernhard Suter, MD, 6701 Fanin St. CCC 1250, Houston, TX 77030, USA.
Email: suter@bcm.edu

features encompass a spectrum of behaviors, such as ataxia, toe walking, hand wringing during ambulation,[6,10] stiff-legged gait,[11,12] freezing of gait,[13] dysrhythmic walking patterns, and lateral and retrograde stepping.[8,14] Downs et al[8] notably contributed to the understanding of motor activities achievable by individuals with Rett syndrome, employing a surveillance video-based movement analysis protocol that highlighted behaviors within natural environmental contexts. Young et al[15] used similar video analysis techniques to delineate walking-associated behaviors in individuals with Rett syndrome during overground and treadmill locomotion. Despite these studies, there remains a dearth of research applying technology-based techniques using quantitative outcome measures.[12,16]

Prior research has demonstrated that promoting an active lifestyle, including participation in walking programs, confers health advantages and enhance quality of life in individuals with Rett syndrome.[9,17] Some potential benefits of improving walking ability in patients with Rett syndrome include reduced spasticity, prevention of foot deformities, and fostering a degree of personal autonomy.[4,6,9,18] Encouragingly, the recent development of genetic interventions designed to ameliorate the symptoms of Rett syndrome may be a great promise in improving gait of individuals with Rett syndrome.[19]

Given the recent emergence of a first drug for Rett,[20] as well as gene-based therapy trials aiming to improve the functional behavior in individuals with Rett syndrome, the development of standardized, quantitative clinical measures capable of cross-site application is imperative. Developing data sets with technology-based gait parameters exhibited by individuals with Rett syndrome is an important and necessary milestone in the process of characterizing the gait of such individuals. Such information can be useful to clinicians and therapists for accurately gauging the efficacy of interventions across diverse research settings.

One-dimensional kinematic metrics have been employed in previous studies to characterize gait in individuals with Rett syndrome, encompassing temporal parameters during both overground and treadmill walking,[16] alongside assessments of knee and hip range of motions, angular velocities, limb asymmetries, and their associated variabilities.[12] However, nonlinear measures have not been reported before. The utilization of nonlinear measures in the analysis of Rett syndrome gait dynamics may offer crucial supplementary insights beyond traditional linear metrics by elucidating complex interactions and patterns within the locomotor system. These nonlinear measures include angle-angle analysis that assesses the coordination patterns between joint angles, providing valuable information about the synchrony of body segments,[21,22] and phase portraits that offer a visual and quantitative representation of the dynamic relationship between angular velocity and angular position.[23] Both metrics capture information across the entire gait cycle, rather than limiting the analysis to discrete points of interest within the gait cycle. As such, the application of such nonlinear metrics to evaluating the gait patterns of patients with Rett syndrome presents itself as a potential means of detecting subtle alterations in gait dynamics over time aiding in the early identification of motor impairment, as well as a more comprehensive way of evaluating of therapeutic interventions in these patients.

This study has 2 objectives. As previously mentioned, it seeks to provide a broader understanding of Rett syndrome gait characteristics beyond traditional linear measures by incorporating nonlinear metrics. Second, it aims to compare the gait features observed in 3 age groups of individuals with Rett syndrome against normative age-based data obtained from healthy populations. By employing these analytical approaches and comparative assessments, this research provides a comprehensive insight into the distinctive gait patterns associated with Rett syndrome and their deviations from typical developmental trajectories observed in healthy individuals.

Materials and Methods

Participants

Twenty-two females diagnosed with Rett syndrome, as per the criteria established by Neul et al,[24] and presenting pathogenic variants in the MECP2 gene, participated in this study. Their ages ranged from 5 to 32 years, with a mean age of 12.6 years and a standard deviation of $\pm$7.4. These individuals were under treatment at the Blue Bird Circle Rett Center at Texas Children's Hospital in Houston, TX. All participants were capable of walking independently without the use of orthotics, and none were prescribed medications known to affect motor control function. Ethical approval for the study was obtained from the Institutional Review Boards of Baylor College of Medicine (H-35835) and the University of Houston (MODCR00000214), and written informed consent was obtained from the parents of the participants. This is a convenience sample of all individuals who have volunteered to participate over the previous 10 years. These data represent the largest sample of individuals with Rett syndrome who have had their gait characteristics assessed using technology-based kinematic measures.

The neurotypical Control data was sourced from the data sets provided by Senden et al,[25,26] which included mean kinematic waveforms for each participant, as well as various spatial and temporal gait parameters. Bilateral sagittal plane kinematic data of the hip, knee, and ankle from 22 neurotypical female individuals who walked on a motorized treadmill were obtained. Their ages ranged from 4 to 32 years, with a mean age of 12.6 years and a

standard deviation of ±7.42 matching the ages of the individuals with Rett syndrome. The Senden data sets were collected with a 16-camera VICON motion analysis system, with joint angles being obtained with the use of Nexus plug-in gait processing software. As noted by the data set authors, "This normative data can be used for comparison of pathological gait, thereby improving the interpretation of pathological gait and finally contributing to better clinical decision making."[25(p3)] For analysis, participants were separated into 3 age groups: 4-8 years, 9-14 years, and 15 years and older. Each age group was age-matched with the same number of neurotypical participants from the database.

Study Protocol

Rett syndrome participants walked on a motorized treadmill (Bertec). Prior to data collection, reflective markers were bilaterally placed on the heel, toe, ankle, knee, shank, and hips. Safety precautions were implemented by securing subjects to an overhead harness, reducing the risk of falls while permitting unrestricted movement during ambulation. The treadmill speed was initiated at 0.1 m/s and was incrementally increased by 0.1 m/s every 20 seconds until either the participants reached their maximum attainable speed, as determined by their physiological responses, or until signs of discomfort, such as vocalizations or manual and facial expressions, were observed. The subjects walked at their maximum attainable comfortable speed for 1-3 minutes depending on every subject's capability and willingness to walk. Kinematic data were collected using a 16-camera VICON motion analysis system at a sampling rate of 100 Hz and processed with the Nexus plug-in gait software to obtain lower limb joint angles. For a more detailed description of the data collection procedures, please refer to Layne et al.[12,27]

Data Processing and Analysis

The data corresponding to the Rett syndrome participants' comfortable speed was analyzed matching the "slow" speed data obtained from the Senden et al data sets. Bilateral sagittal plane flexion angles for the hips, knees, and ankles were obtained and filtered using a second-order Butterworth filter with a 6-Hz cutoff frequency. The time series joint angle data were then precisely segmented at the peak knee flexion point. This approach was necessary because of the observation of numerous strides lacking heel strikes (ie, toe walking). Peak knee flexion served as a consistent kinematic marker within each stride and was therefore used as the reference point for identifying individual strides.[28]

Each identified gait cycle was then uniformly time-normalized to 100 samples, ensuring standardization across subjects and improving the reliability of comparative analyses. Mean waveforms for each limb and joint of each individual were subsequently calculated. The individual mean waveforms of the control group, also standardized to 100 samples, were aligned such that the initial sample corresponded to peak knee flexion (see Results). All the processing and analysis described in this section were performed using custom MATLAB scripts.

Linear Measures

The range of motion for each joint was calculated by measuring the difference in degrees between the minimum and maximum angles observed throughout the gait cycle. This metric offers a precise quantification of the joint's movement extent, enabling detailed comparisons of joint mobility across various conditions or subjects.

The side exhibiting the greatest knee range of motion was designated as the "greater" side, whereas the opposite side was labeled as the "lesser" side. For subsequent analyses, the data were classified according to this designation, allowing comparisons between the side with the greater knee range of motion and the side with the lesser knee range of motion. This approach enabled a more detailed examination of asymmetries and their potential impact on gait dynamics.

Stride time was calculated as the average time interval between consecutive peak knee flexion events before temporal normalization. The average stride time for each individual in the Control group was presented in the normative data set enabling calculation of grand means for each age group. Peak angular velocity was calculated using the mean waveforms of each participant for each side and joint.

Nonlinear Measures

Angle-angle diagrams, as described by Goswami,[21] were generated for each subject using their corresponding mean waveforms to visualize the relationships between hip-knee and knee-angle flexion angles throughout the gait cycle. The area enclosed by the angle-angle loops was calculated.[28]

Phase portraits, as described by Hurmuzlu,[23] were created to illustrate the relationship between angular velocity and angular position for each joint, for every subject. These portraits offered insights into the dynamic stability and control mechanisms during gait. The area of the phase portrait loops was calculated, allowing for a precise assessment of the joint's dynamic behavior throughout the gait cycle. The areas of the angle-angle and phase portrait loops were calculated using a custom MATLAB script.

Symmetry Index

Symmetry Indexes between the greater X_G and lesser side X_L were calculated for each outcome measure for each subject, using the following formula.

$$SI = \frac{|X_G - X_L|}{0.5 \cdot (X_G + X_L)} \cdot 100\%$$

A Symmetry Index of 0 indicates perfect symmetry between the 2 limbs.

Overall Symmetry Index

Mean waveforms were calculated for each age group. To compare the symmetry of the waveforms for each joint between the 2 legs, we computed an Overall Symmetry Index using the formula proposed by Nigg et al.[29,30]

$$OSI = \int_{t=1}^{100} A|x_g(t) - x_l(t)|dt$$

$$A = \frac{2}{range(x_g(t)) + range(x_l(t))}$$

where OSI is the Overall Symmetry Index, $x_g(t)$ is the value of the joint angle recorded for the greater leg at the time t and $x_l(t)$ the joint angle recorded for the lesser leg at the time t. The integrand of Eq. (2) is referred to as the symmetry function and provides information on the time dependency of symmetry over the 100 time points of the gait cycle. The closer the Symmetry Index value is to zero, the more symmetric the gait. The range is used instead of the mean in order to normalize the symmetry index since the range is not dependent on the reference joint position.

Statistical Analysis

Grand means plus one standard deviation (SD) were obtained for each variable of each age group. Because of the limited number of participants in each group thereby making more traditional statistical testing problematics, a 95% confidence interval (CI) for each variable and joint of the 3 Control groups was calculated. To compare the similarity between the Rett syndrome and control data we compared the Rett syndrome mean values against the Control CI.

Pearson r correlations between the mean waveforms of the Rett syndrome group and the Control group were computed to assess the similarity in waveform shape. The percentage of samples of the mean waveforms of the Rett syndrome group that fell outside the Control CIs was then computed, providing an assessment of how closely the amplitudes of the participants' waveforms matched those of the Controls across the entire waveform.

Table 1. Rett syndrome Subject Characteristics.

Subject	Age (y)	Height (cm)	Body weight (kg)	Scoliosis
1	5	97.0	15.2	Mild (24 degrees)
2	5	103.0	16.3	No scoliosis
3	5	96.5	13.2	No scoliosis
4	6	101.0	18.3	No scoliosis
5	7	122.5	30.2	No scoliosis
6	7	111.0	15.0	No scoliosis
7	8	130.0	30.2	Moderate (37 degrees)
8	8	122.2	22.0	Mild (15 degrees)
9	9	137.5	27.8	Mild (17 degrees)
10	9	130.0	23.6	Mild (16 degrees)
11	10	134.0	23.7	Moderate (34 degrees)
12	10	129.5	24.0	No scoliosis
13	11	137.2	31.8	No clear scoliosis (last MR showed mild curvature)
14	12	145.8	50.1	Severe (44 degrees)
15	15	140.0	36.0	Moderate (25)
16	16	139.8	47.2	Severe (45 degrees)
17	17	136.2	46.3	Severe (57 degrees)
18	19	158.0	44.0	Moderate (32 degrees)
19	20	147.0	43.0	Post scoliosis surgery
20	20	147.0	90.7	No scoliosis
21	27	140.0	32.0	2 rods placed in 2011
22	32	139	40	Moderate (35 degrees)

Table 2. Mean Treadmill Speed by Age Group and Condition.

Age group	Speed, m/s		
	RTT, mean (SD)	Control, mean (SD)	Control, CI
4-8 y	0.5 (0.1)*	0.9 (0.1)	0.8-1.0
9-14 y	0.5 (0.2)*	0.9 (0.1)	0.8-1.0
>15 y	0.6 (0.1)*	0.9 (0.1)	0.8-0.9

Abbreviations: CI, confidence interval; RTT, Rett syndrome; SD, standard deviation.
* participant's mean value is outside the confidence interval bounds of the Control data.

Results

The data from 44 participants were analyzed, 22 neurotypical female individuals and 22 females diagnosed with Rett syndrome. The participants were separated into 3 age groups: 4-8-year-olds (8 participants), 9-14-year-olds (6 participants), and those aged 15 years and older (8 participants). Each of the age groups contained the same number of Rett syndrome and Control participants. The data from the lesser ankle joint of 1 participant in the 9-14-year age group was removed because of a technical issue during data collection.

Table 3. Mean Stride Time and Stride Length by Age Group and Condition.

		Stride time, s			Stride length, m		
Age group	Side	RTT, mean (SD)	Control, mean (SD)	Control, CI	RTT, mean (SD)	Control, mean (SD)	Control, CI
4-8 y	Greater	1.1 (0.2)*	1.0 (0.1)	0.9 to 1.0	0.6 (0.1)*	0.8 (0.1)	0.8 to 0.9
	Lesser	1.1 (0.2)*	1.0 (0.1)	0.9 to 1.0	0.6 (0.1)*	0.8 (0.1)	0.8 to 0.9
9-14 y	Greater	1.2 (0.3)	1.1 (0.1)	1.0 to 1.2	0.6 (0.2)*	1.0 (0.1)	0.9 to 1.0
	Lesser	1.2 (0.2)	1.1 (0.1)	1.0 to 1.2	0.6 (0.2)*	1.0 (0.1)	0.9 to 1.0
15 y	Greater	1.2 (0.3)	1.3 (0.1)	1.2 to 1.4	0.7 (0.2)*	1.1 (0.1)	1.0 to 1.2
	Lesser	1.2 (0.3)	1.3 (0.1)	1.2 to 1.4	0.7 (0.2)*	1.1 (0.1)	1.0 to 1.2
Age group		Stride time Symmetry Index			Stride length Symmetry Index		
4-8 y		1.3 (1.7)*	0.0 (0.0)	0.0 to 0.0	1.3 (1.7)*	0.0 (0.0)	0.0 to 0.0
9-14 y		1.4 (1.7)*	0.0 (0.0)	0.0 to 0.0	1.4 (1.7)*	0.2 (0.4)	–0.2 to 0.5
>15 y		0.8 (1.0)*	0.0 (0.0)	0.0 to 0.0	0.8 (1.0)*	0.0 (0.0)	0.0 to 0.0

Abbreviations: CI, confidence interval; RTT, Rett syndrome.
* participant's mean value is outside the confidence interval bounds of the Control data.

The mean age for 4-8 years old Control group was 6.3 years (SD = 1.5), whereas the Rett syndrome group had a mean of 6.3 years (SD = 1.3). In the 9-14-year age group, both the Control and Rett syndrome groups shared identical mean ages of 10.2 years (SD = 1.2). For participants over 15 years old, the Control group had a mean age of 20.9 years (SD = 5.7), and the Rett syndrome group had a mean of 20.8 years (SD = 5.9). Table 1 presents a description of the Rett syndrome subjects' characteristics. All individuals with Rett syndrome presented ataxic gait and at least mildly increased tone, typical of Rett syndrome, in the lower extremities, especially at the ankles, at baseline. No marked tone asymmetries were found in these individuals. The degree of scoliosis varied across participants, with Cobb angles ranging from 0° to 57° (Table 1).

Rett syndrome participants walked at a slower speed compared with the Control group across the 3 age groups (Table 2). Table 3 displays the mean stride time and stride length for the 3 age groups, comparing participants with Rett syndrome condition with those in the Control group. The individuals with Rett syndrome in the 4- to 8-year-old age group had greater stride times than those in the Control group. Stride times between Rett syndrome and Controls for 9-14-year-olds and >15-year-olds were similar. Stride length was shorter in the Rett syndrome participants across the 3 age groups, and they also showed a greater asymmetry on both stride time and stride length compared with the Control group.

Tables 4 and 5 show the mean and standard deviation categorized by age group, condition (Rett syndrome vs Control), and limb (greater vs lesser limbs) of the range of motion and peak velocity, respectively. Mean Symmetry Indexes of each parameter are also included and 95% confidence intervals (CIs) for the Control group are provided to show the range within which the mean of the Control group likely falls.

Across all age groups, individuals with Rett syndrome consistently exhibited less mean hip and knee range of motion compared with Control participants. In the ankle joint, the 4-8-year-olds and >15-year-olds showed less range of motion than Control participants, whereas the ankle range of motion of the 9-14-year-old group fell between the CI of the ankle range of motion of the Control group. Rett syndrome participants showed greater range of motion asymmetry compared to Controls for all comparisons, except for the 9-14-year-old age group's ankle Symmetry Index.

Rett syndrome participants demonstrated significantly lower hip and knee peak velocity across all age groups and significantly lower ankle peak velocity in the 4-8-year and ≥15-year age groups compared with Control participants. The ankle peak velocity values of both limbs of the 9-14-year age group were similar to the Controls. Moreover, Rett syndrome participants showed higher asymmetry in their peak velocity Symmetry Index values across all joints and age groups compared with Control participants, except for the 9-14-year age group's ankle Symmetry Index.

Waveforms Analysis

Table 6 shows the Overall Symmetry Index values between both legs over the complete gait cycle. individuals with Rett syndrome showed greater asymmetry compared with the Control group participants across all joints and age groups.

Figures 1-3 contain the Rett syndrome and Control time series mean waveforms for each joint and limb for the 3 different age groups. The Pearson correlation coefficients (r) between the Rett syndrome and Control groups' mean waveforms are included. Additionally, the percentage of Rett syndrome mean waveform samples that fall

Table 4. Mean Range of Motion by Age Group and Condition.

		Hip ROM, degrees			Knee ROM, degrees			Ankle ROM, degrees		
Age group	Side	RTT, mean (SD)	Control, mean (SD)	Control, CI	RTT, mean (SD)	Control, mean (SD)	Control, CI	RTT, mean (SD)	Control, mean (SD)	Control, CI
4-8 y	Greater	34.1 (4.9) *	43.2 (4.9)	39.8-46.6	46.1 (2.7)*	69.0 (3.0)	66.9-71.0	18.7 (4.8) *	24.1 (3.8)	21.5-26.7
	Lesser	33.4 (5.3) *	42.5 (1.9)	41.2-43.9	34.9 (6.5) *	65.2 (3.5)	62.8-67.6	18.0 (7.9) *	24.4 (6.1)	20.1-28.6
9-14 y	Greater	34.1 (4.3) *	42.3 (5.3)	38.1-46.6	44.3 (9.0) *	65.4 (5.4)	61.1-69.7	22.3 (12.4)	24.5 (7.1)	18.8-30.1
	Lesser	33.8 (9.1) *	42.5 (5.2)	38.4-46.7	39.3 (8.9) *	63.9 (4.6)	60.2-67.6	23.2 (9.6)	23.4 (4.9)	19.5-27.3
≥15 y	Greater	29.9 (6.5) *	41.3 (4.1)	38.4-44.2	39.1 (8.0) *	62.3 (4.7)	59.1-65.6	17.7 (3.2) *	25.1 (2.9)	23.1-27.1
	Lesser	29.5 (8.7) *	40.5 (4.6)	37.3-43.7	29.1 (9.7) *	59.7 (3.6)	57.2-62.3	15.7 (7.7) *	26.9 (5.9)	22.8-31.0
Age group		Hip ROM Symmetry Index			Knee ROM Symmetry Index			Ankle ROM Symmetry Index		
4-8 y		9.9 (7.2)	6.9 (5.5)	3.1-10.7	28.9 (18.5) *	5.7 (4.4)	2.7-8.7	37.1 (38.5) *	15.3 (12.6)	6.6-24.0
9-14 y		14.0 (5.9) *	3.1 (2.2)	1.3-4.9	12.1 (9.9) *	2.3 (1.9)	0.8-3.8	11.0 (9.2)	10.4 (8.9)	3.2-17.5
≥15 y		16.8 (12.7) *	6.3 (4.5)	3.2-9.4	32.1 (28.1) *	4.2 (4.1)	1.3-7.0	33.7 (32.7) *	12.2 (9.0)	5.9-18.4

Abbreviations: CI, confidence interval; ROM, range of motion; RTT, Rett syndrome.
* participant's mean value is outside the confidence interval bounds of the Control data.

Table 5. Mean Peak Velocity by Age Group and Condition.

		Hip peak velocity, degrees / % of gait cycle			Knee peak velocity, degrees / % of gait cycle			Ankle peak velocity, degrees / % of gait cycle		
Age group	Side	RTT, mean (SD)	Control, mean (SD)	Control, CI	RTT, mean (SD)	Control, mean (SD)	Control, CI	RTT, mean (SD)	Control, mean (SD)	Control, CI
4-8 y	Greater	176.4 (39.5) *	225.4 (29.5)	204.9-245.8	289.4 (27.3) *	383.3 (26.0)	365.3-401.4	88.9 (31.4) *	138.7 (28.6)	118.9-158.5
	Lesser	157.2 (30.7) *	217.8 (13.0)	208.8-226.7	251.2 (68.2) *	365.5 (23.9)	348.9-382.0	78.4 (40.9) *	133.2 (36.7)	107.7-158.6
9-14 y	Greater	191.7 (74.6) *	224.1 (16.7)	210.7-237.4	304.1 (59.4) *	384.6 (40.5)	352.1-417.0	123.8 (59.4)	133.6 (48.2)	95.0-172.2
	Lesser	166.6 (42.3) *	227.6 (26.6)	206.3-248.9	256.8 (74.0) *	376.1 (36.3)	347.1-405.1	114.9 (45.2)	124.5 (26.1)	103.6-145.4
≥15 y	Greater	142.6 (23.4)*	214.8 (15.5)	204.1-225.6	254.8 (64.1) *	382.9 (15.5)	372.1-393.6	87.3 (20.1) *	158.3 (21.7)	143.3-173.3
	Lesser	146.5 (41.9) *	217.7 (18.1)	205.2-230.2	206.7 (64.3) *	382.0 (15.3)	371.4-392.6	105.7 (60.1) *	170.6 (45.0)	139.4-201.7
Age group		Hip peak velocity Symmetry Index			Knee peak velocity Symmetry Index			Ankle peak velocity Symmetry Index		
4-8 y		19.4 (14.2) *	6.2 (6.3)	1.8-10.6	23.0 (23.9) *	6.3 (5.2)	2.7-9.9	42.2 (37.2) *	18.7 (17.6)	6.5-30.9
9-14 y		27.4 (22.8) *	5.3 (4.3)	1.8-8.8	18.4 (15.7) *	3.4 (2.2)	1.6-5.1	21.0 (21.3)	16.6 (15.9)	3.8-29.3
≥15 y		15.5 (16.0) *	9.1 (4.1)	6.3-12.0	22.1 (13.1) *	3.7 (2.3)	2.1-5.3	45.5 (39.6) *	17.5 (13.9)	7.8-27.1

Abbreviation: CI, confidence interval; RTT, Rett syndrome.
* participant's mean value is outside the confidence interval bounds of the Control data.

Table 6. Overall Symmetry Index Over the Complete Gait Cycle by Age Group and Condition.

	Hip overall Symmetry Index			Knee overall Symmetry Index			Ankle overall Symmetry Index		
Age group	RTT, mean (SD)	Control, mean (SD)	Control, CI	RTT, mean (SD)	Control, mean (SD)	Control, CI	RTT, mean (SD)	Control, mean (SD)	Control, CI
4-8	17.1 (7.9)*	5.5 (2.7)	3.6-7.3	35.5 (26.5)*	4.3 (1.9)	3.0-5.7	67.6 (53.4)*	14.7 (6.2)	10.4-19.0
9-14	17.2 (9.9)*	3.8 (1.2)	2.9-4.8	21.6 (19.2)*	3.0 (1.0)	2.2-3.9	28.5 (21.1)*	6.4 (2.1)	4.7-8.1
≥15	16.8 (6.0)*	4.2 (2.0)	2.8-5.6	22.5 (5.7)*	5.1 (2.6)	3.3-6.9	30.8 (14.9)*	9.6 (2.6)	7.8-11.5

Abbreviation: CI, confidence interval; RTT, Rett syndrome.
* participant's mean value is outside the confidence interval bounds of the Control data.

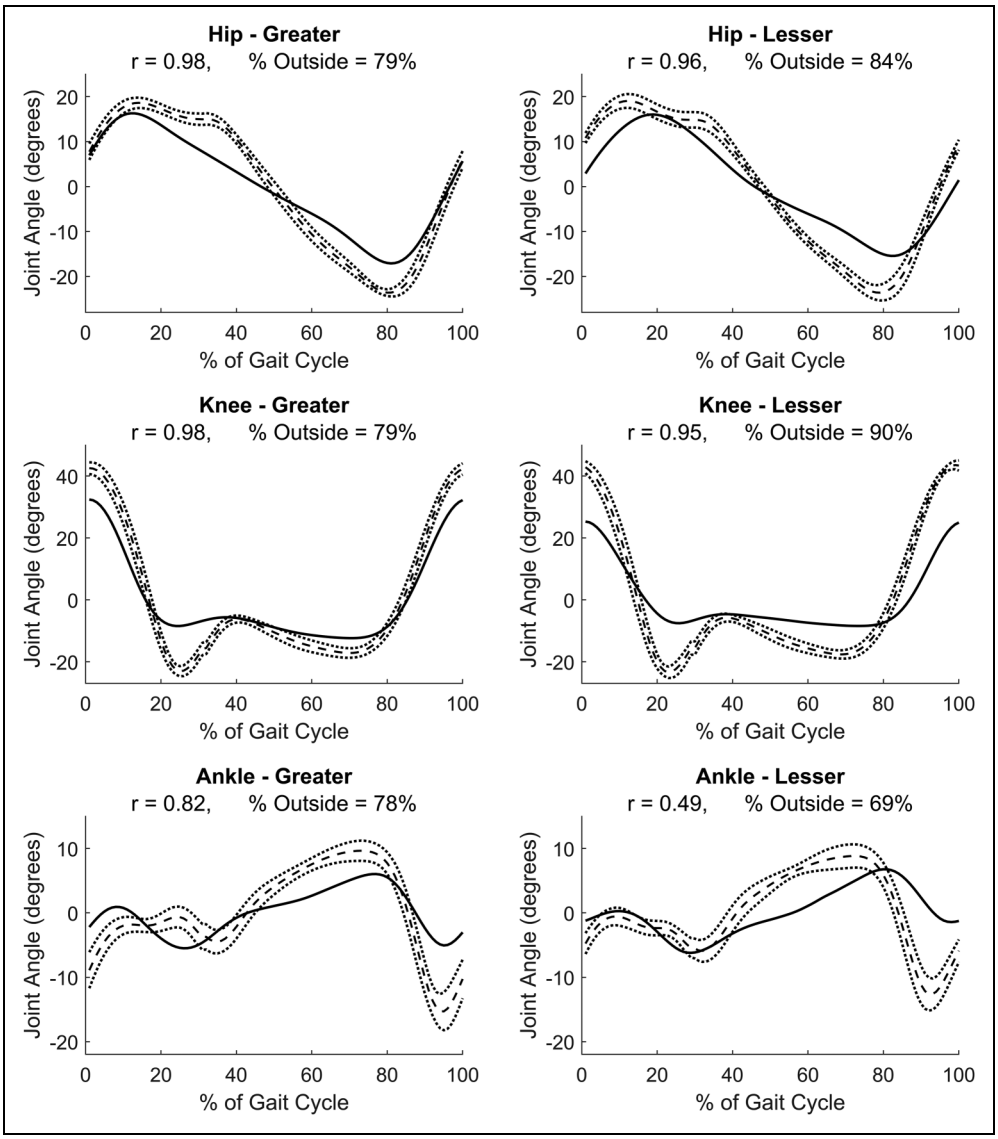

Figure 1. Mean waveforms: Rett vs Control, 4-8 years old. Rett syndrome mean waveforms are shown in solid lines and Control mean waveforms are shown in dashed lines. Dotted lines represent the upper and lower limits of the 95% CI of the Control group. Pearson *r* correlation coefficient between the Rett syndrome and Control groups' mean waveforms. % Outside = Percentage of Rett syndrome mean waveform samples that fall outside the Control group's confidence interval.

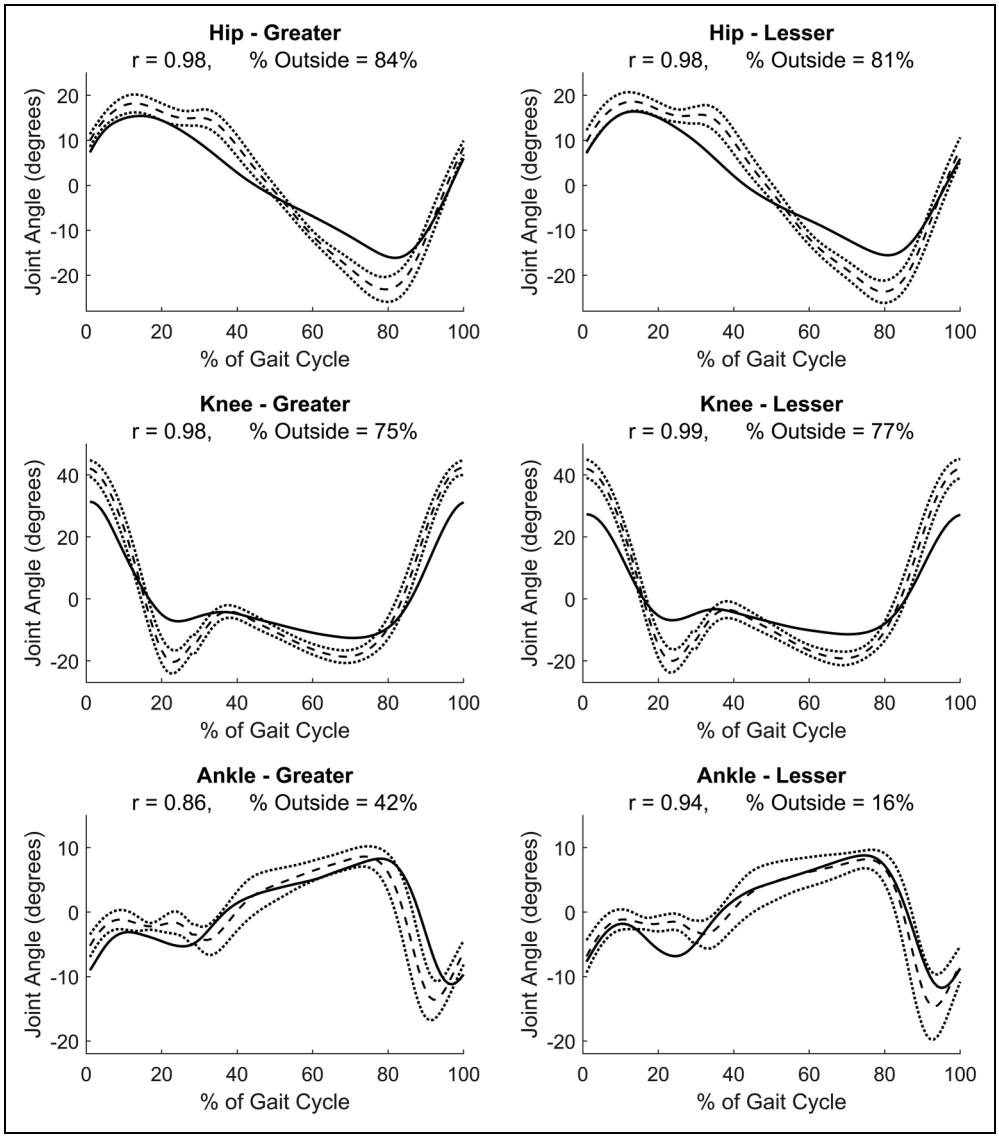

Figure 2. Mean waveforms: Rett vs Control, 9-14 years old. Rett syndrome mean waveforms are shown in solid lines and Control mean waveforms are shown in dashed lines. Dotted lines represent the upper and lower limits of the 95% CI of the Control group. Pearson *r* correlation coefficient between the Rett syndrome and Control groups' mean waveforms. % Outside = Percentage of Rett syndrome mean waveform samples that fall outside the Control group's confidence interval.

outside the Control group's CIs are displayed, providing insights into the deviations in gait patterns. The mean waveforms have been amplitude normalized to have a mean of zero, allowing for direct comparison of their relative shapes.

For the hip, high correlation values ($r = 0.96$-0.98) are observed across all age groups, indicating that the overall waveform pattern of individuals with Rett syndrome closely aligns with that of the Control group. However, the percentage of samples outside the Control CI is higher for older participants, with 90% and 88% of samples for the greater and lesser limbs in the ≥15 age group falling outside the Control CI. This percentage decreases in younger age groups, indicating a greater deviation in the hip movement pattern with age. Similar to the hip, the knee joint exhibits strong correlation values ($r = 0.95$-0.99) across all age groups, suggesting that knee movement in Rett syndrome participants closely mirrors those of Controls. However, although the overall movement patterns are similar, the range of motion in Rett syndrome participants is noticeably smaller. This reduced amplitude of knee joint movement in Rett syndrome causes an elevated percentage of the Rett syndrome mean waveform to fall outside the Control, especially in the 4-8-year age group, with values reaching as high as 90% in the 4-8 "lesser" limb. Correlation values for the ankle joint are lower than those of the hip and knee, especially in the 4-8 age group, where r values drop to 0.49 for the lesser limb.

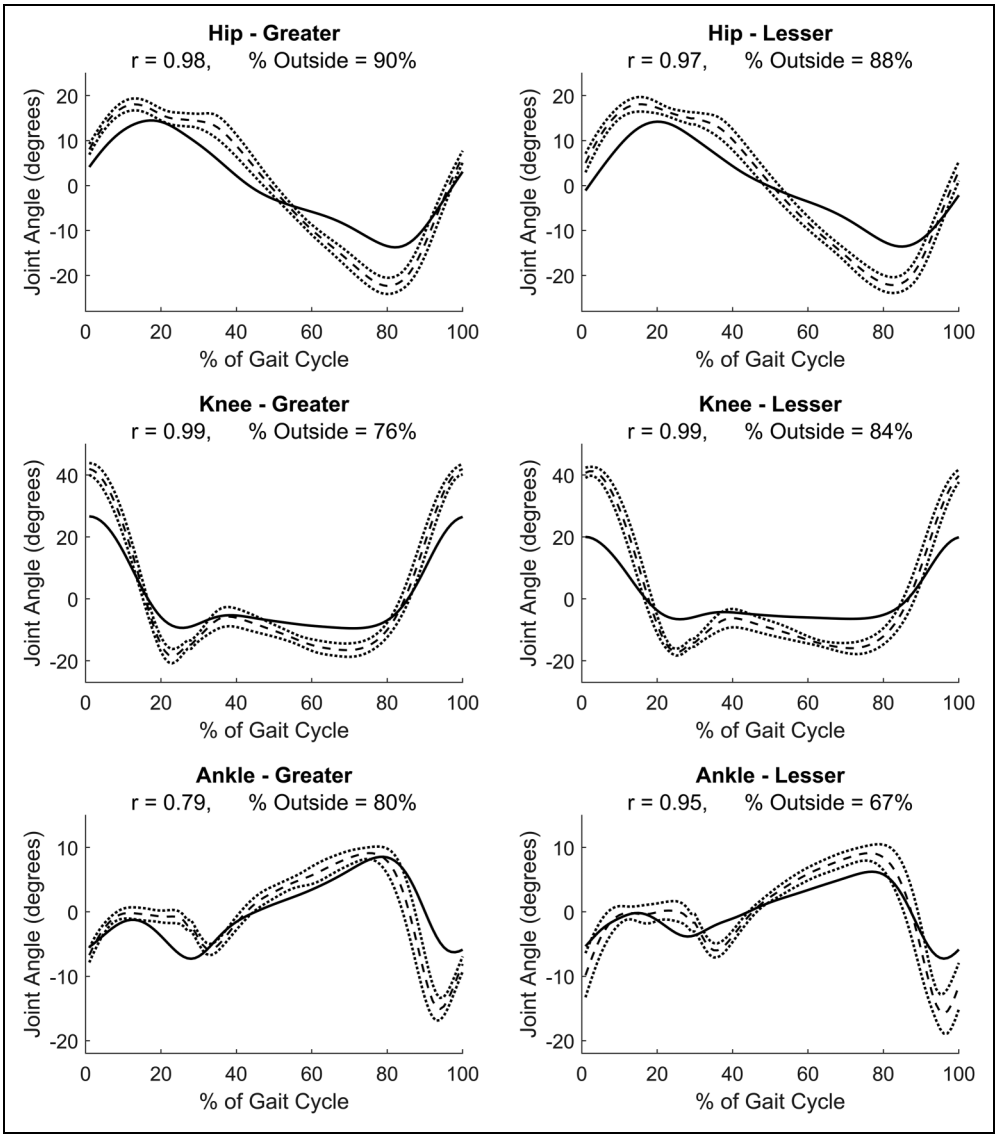

Figure 3. Mean waveforms: Rett vs Control, ≥15 years old. Rett syndrome mean waveforms are shown in solid lines and Control mean waveforms are shown in dashed lines. Dotted lines represent the upper and lower limits of the 95% CI of the Control group. Pearson *r* correlation coefficient between the Rett syndrome and Control groups' mean waveforms. % Outside = Percentage of Rett syndrome mean waveform samples that fall outside the Control group's confidence interval.

The percentage of samples outside the Control CI is more variable for the ankle joint, ranging from 42% to 80% of samples fall outside the Control CI, highlighting significant differences in ankle movement patterns between Rett syndrome participants and Controls.

Phase Portraits

Figures 4-6 display the Rett syndrome and Control phase portraits for each joint and limb for the 4-8-year, 9-14-year, and ≥15-year age groups respectively. These figures were developed from the mean joint waveforms. Table 7 contains a summary of the phase portrait areas grouped by age group, condition (Rett syndrome vs Control), and limb (greater vs lesser limbs). Ninety-five percent CIs for the Control group are also provided. The Symmetry Index between the phase portrait areas of the "greater" and "lesser" limbs are also included in this table.

Both the figures and Table 7 show that the Rett syndrome phase portraits of the hip and knee joints are significantly smaller compared with the Control phase portraits, but with the shape remaining similar. In contrast, the Rett syndrome ankle phase portraits display a greater variability in shape, especially in the 4-8-year-olds. Compared with the Control group, the ankle phase portrait area of both limbs of the 4-8-year and ≥15-year groups are smaller, but the ankle phase portrait areas of both limbs of the 9-14-year-olds fall inside

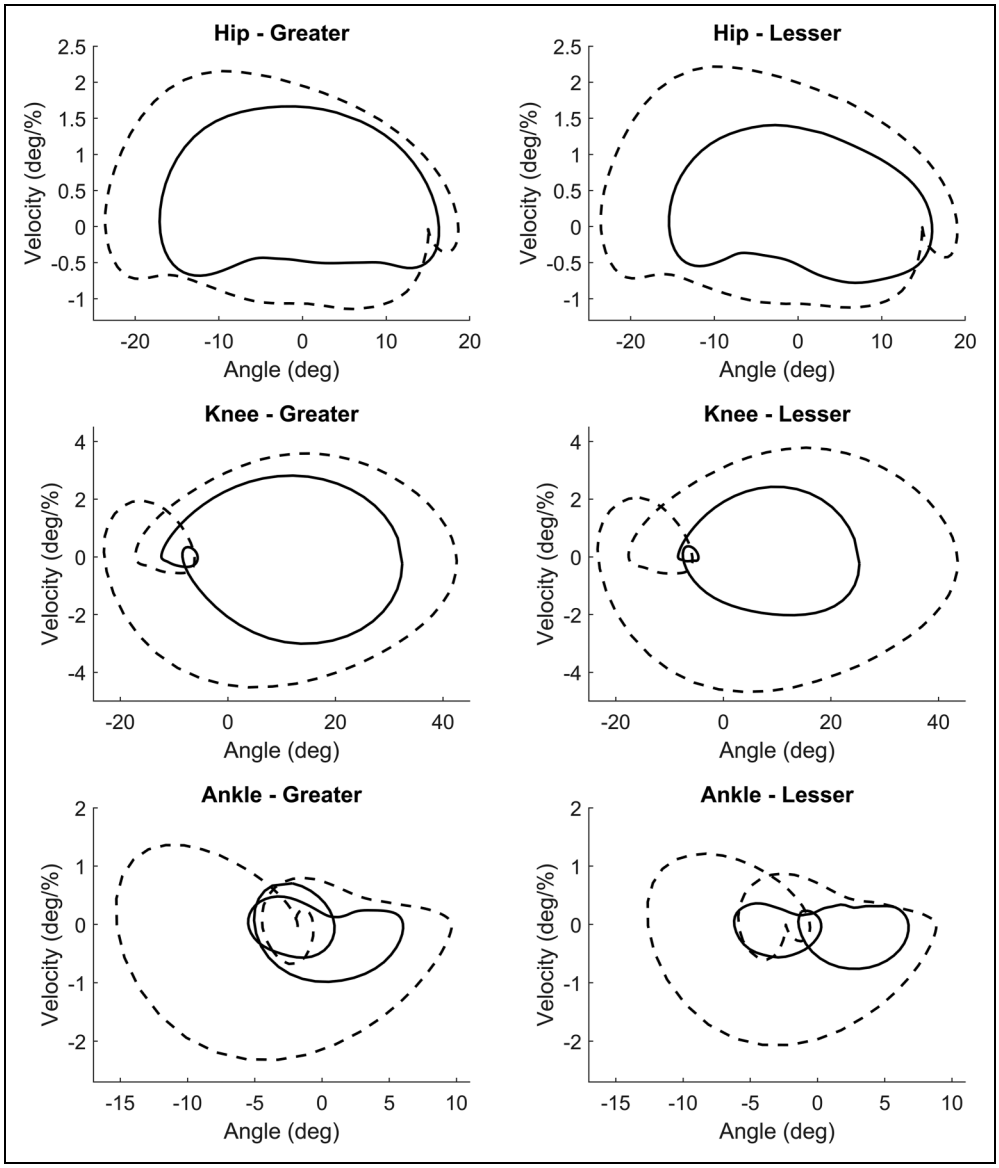

Figure 4. Rett vs Control phase portraits, 4-8 years old. Rett Syndrome Portraits are shown in solid lines, and Control portraits are shown in dashed lines. The joint angle mean waveforms have been shifted tohave a mean of zero, allowing for direct comparison of their relative shapes.

the Control CIs for that same age group. Rett syndrome participants showed higher phase portrait area asymmetry compared with Controls across all joints and age groups, with the exception of the ankle joint in the 9-14-year age group.

Angle-Angle Diagrams

Figures 7-9 display the Rett syndrome and Control angle-angle diagrams for each joint and limb for the 4-8-year, 9-14-year, and ≥15-year age groups, respectively. Table 8 presents a summary of the angle-angle diagram areas grouped by age group, condition (Rett syndrome vs Control) and Limb (greater vs lesser limbs) and include the 95% CI for the Control group. The Symmetry Index between the angle-angle diagram areas of the "greater" and "lesser" limbs is also included in Table 8.

Rett syndrome angle-angle diagrams are significantly smaller compared to the Controls across all age groups, despite similar shapes. Rett syndrome knee vs ankle diagrams display a greater shape variability compared with the hip vs knee diagrams. For both hip vs knee and knee vs ankle, the "lesser" limb has a smaller area compared to the "greater limb." In the 3 age groups, Rett syndrome participants showed higher asymmetry in their angle-angle areas compared with Controls.

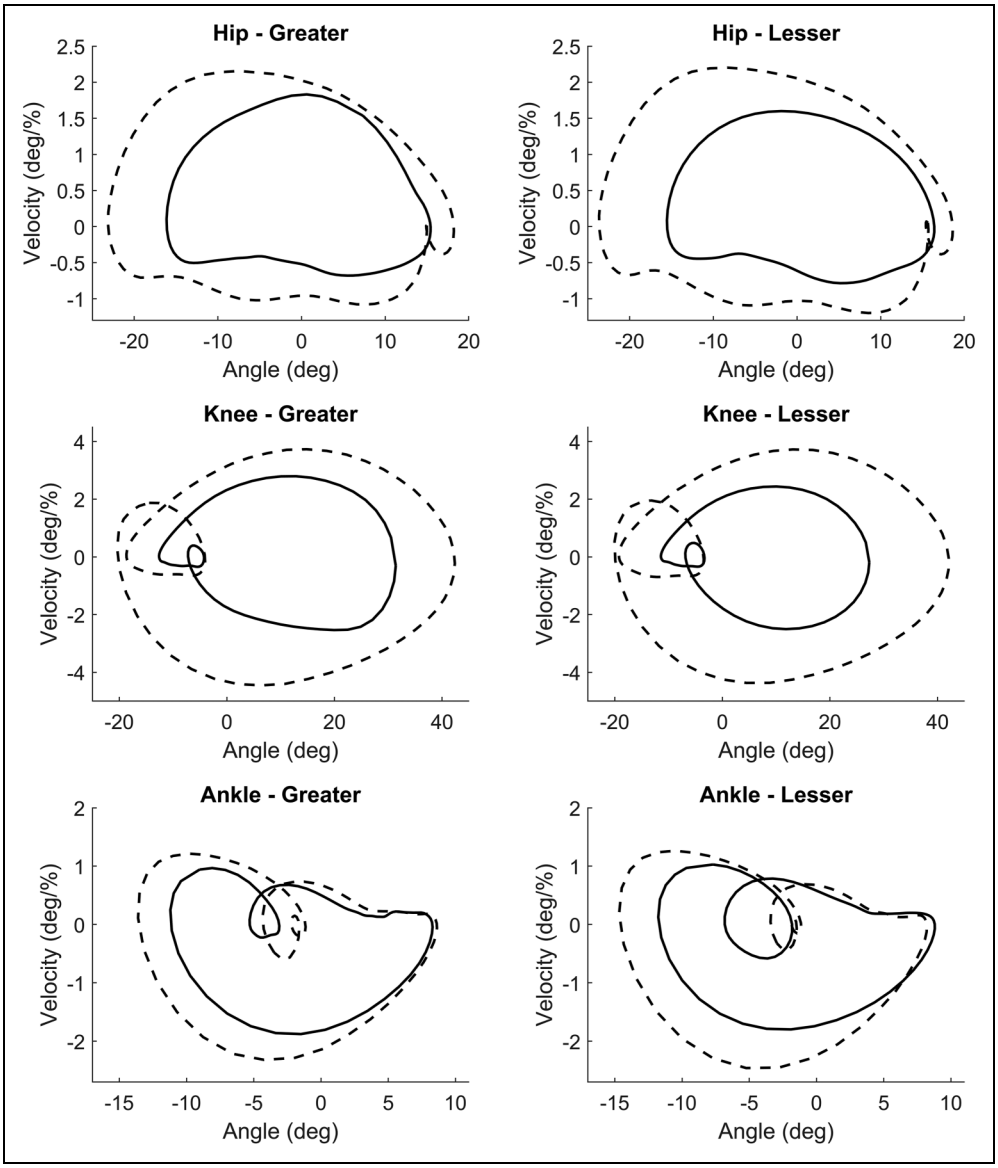

Figure 5. Rett vs Control phase portraits, 9-14 years old. Rett syndrome portraits are shown in solid lines, and control portraits are shown in dashed lines. The joint angle mean waveforms have been shifted to have a mean of zero, allowing for direct comparison of their relative shapes.

Discussion

Gait quality can be a reliable marker of overall health in neurotypical individuals and is strongly associated with the severity of neurodevelopmental disorders.[31,32] Accurately measuring gait metrics in individuals with Rett syndrome can offer significant insights into their overall health status. Therefore, it is important to use a comprehensive set of measures to assess gait in patients with Rett syndrome. These metrics, when combined with traditional motor assessments, can provide a more detailed understanding of their locomotor abilities.

The combined use of both linear and nonlinear gait measures offers a more in-depth analysis of specific gait features that could be targeted to enhance gait efficiency. This approach can detect subtle changes in gait patterns over time or in response to interventions, whether they involve physical therapy, medications, or genetic therapies. For example, even when the range of motion of 2 joints may be similar, angle-angle diagrams may reflect different coordination patterns.

The primary aim of this study was to provide a broader characterization of walking behavior in individuals with Rett syndrome by using technology-based linear and nonlinear metrics. Additionally, we aimed to explore potential differences when compared to age-matched neurotypical individuals and to investigate whether any observed differences in

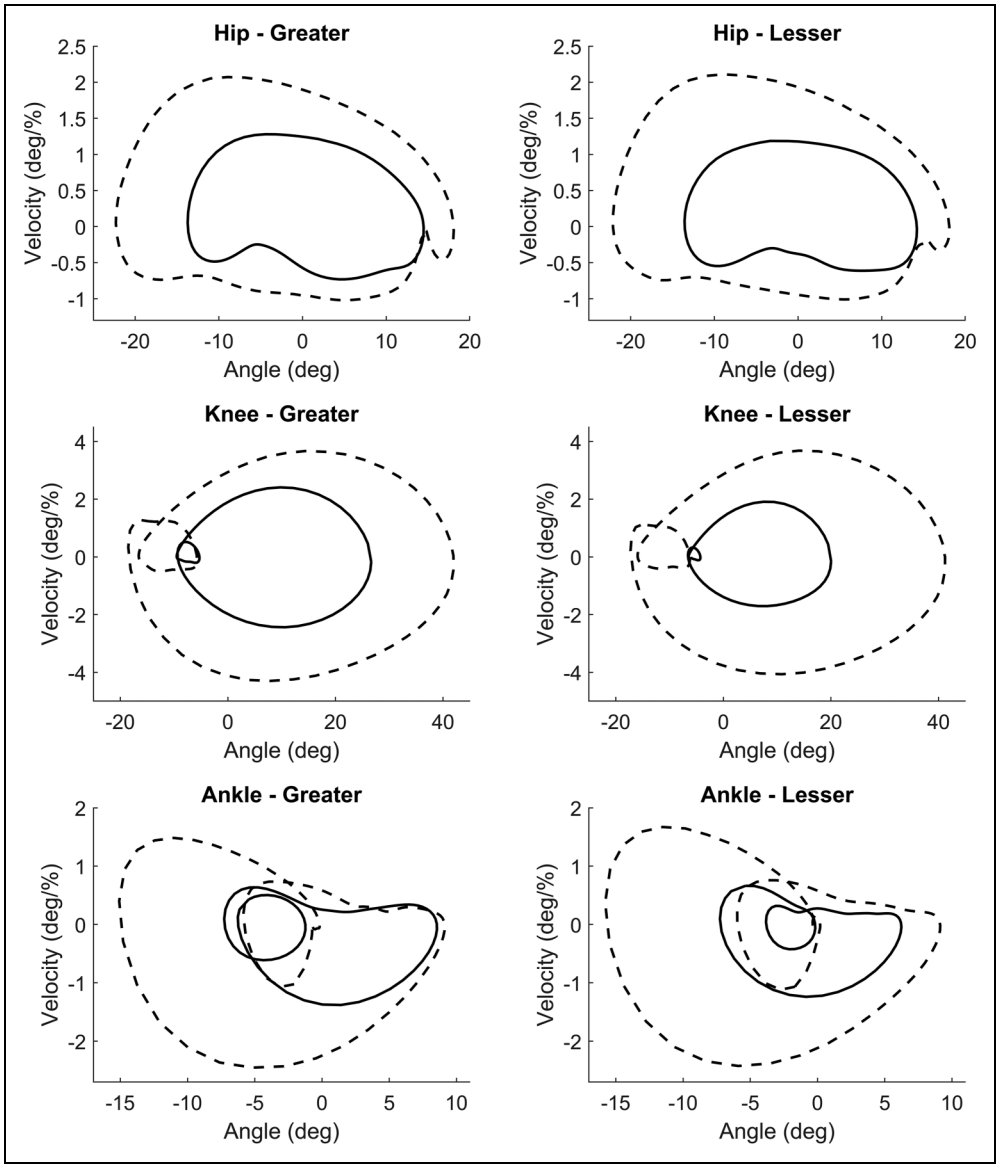

Figure 6. Rett vs Control phase portraits, ≥15 years old. Rett syndrome portraits are shown in solid lines, and Control portraits are shown in dashed lines. The joint angle mean waveforms have been shifted to have a mean of zero, allowing for direct comparison of their relative shapes.

walking behavior were influenced by age. This research is the first to provide technology-based nonlinear gait measurements for patients with Rett syndrome, with the anticipation that these data will serve as a foundation for future studies.

Our findings revealed that despite comparable stride times between individuals with Rett syndrome and neurotypical individuals, several kinematic measures demonstrated reduced joint motion amplitude and velocity in individuals with Rett syndrome, which was also reflected in their reduced stride length and walking speed (Tables 2 and 3). Interestingly, these reductions occurred despite the temporal features of the kinematic waveforms displaying a high degree of similarity.

Figures 1-3 display that there were consistent differences in the amplitude of the joint waveforms at all ages between Rett syndrome and neurotypical individuals, but the overall shape of their kinematic waveforms remained similar. This is especially true at the hip and knee, which displayed very high correlations ($r \geq 0.95$). This indicates that despite reductions in amplitude, individuals with Rett syndrome retained the temporal pattern of joint motion demonstrated by healthy, age-matched Control participants. For example, the time behavioral events of peak knee extension or peak hip flexion within the gait cycle were nearly identical to those of the age-matched neurotypical individuals, revealing that the underlying features of

Table 7. Mean Phase Portrait Areas by Age Group and Condition.

Age group	Side	Hip phase portrait area, degrees^2 / % of gait cycle			Knee phase portrait area, degrees^2 / % of gait cycle			Ankle phase portrait area, degrees^2 / % of gait cycle		
		RTT, mean (SD)	Control, mean (SD)	Control, CI	RTT, mean (SD)	Control, mean (SD)	Control, CI	RTT, mean (SD)	Control, mean (SD)	Control, CI
4-8 y	Greater	69.4 (20.9) *	112.4 (25.6)	94.7-130.2	203.9 (19.9) *	471.0 (41.7)	442.1-499.9	34.0 (19.3) *	67.4 (13.6)	57.9-76.8
	Lesser	61.2 (18.8) *	105.5 (9.7)	98.7-112.2	128.0 (49.6) *	412.9 (48.6)	379.2-446.5	30.5 (21.3) *	69.2 (26.0)	51.2-87.3
9-14 y	Greater	70.5 (16.4) *	109.3 (26.3)	88.3-130.4	206.3 (85.1) *	438.9 (97.3)	361.1-516.8	62.9 (59.5)	71.1 (31.6)	45.8-96.3
	Lesser	67.1 (31.7) *	110.2 (26.2)	89.2-131.1	153.1 (73.4) *	412.7 (77.4)	350.7-474.6	62.9 (51.0)	64.9 (17.9)	50.5-79.2
≥15 y	Greater	51.3 (21.8) *	101.0 (22.5)	85.4-116.6	152.6 (65.8) *	399.0 (73.8)	347.9-450.2	34.8 (12.6) *	80.7 (22.1)	65.4-96.0
	Lesser	52.5 (29.3) *	98.6 (20.1)	84.7-112.6	89.1 (53.2) *	368.4 (46.3)	336.3-400.5	39.1 (35.9) *	94.0 (39.5)	66.6-121.3
Age group		Hip peak velocity Symmetry Index			Knee phase portrait area Symmetry Index			Ankle phase portrait area Symmetry Index		
4-8 y		22.6 (19.4) *	12.7 (9.7)	5.9-19.4	51.3 (37.4) *	13.4 (8.8)	7.4-19.5	64.6 (48.5) *	22.9 (18.9)	9.8-36.0
9-14 y		29.3 (19.5) *	6.8 (5.5)	2.4-11.3	31.1 (21.4) *	5.9 (4.6)	2.2-9.6	17.7 (17.3)	16.6 (17.5)	2.6-30.5
≥15 y		32.3 (29.1) *	11.3 (8.1)	5.6-16.9	59.9 (28.6) *	7.7 (8.2)	2.0-13.4	78.6 (40.6) *	18.9 (13.2)	9.7-28.1

Abbreviation: CI, Confidence Interval; RTT, Rett syndrome.
* participant's mean value is outside the confidence interval bounds of the Control data.

gait motor control remain intact in these individuals with Rett syndrome.

Similar reductions in joint range of motion and angular velocity have been previously reported in Rett syndrome[12,33] and in other neurodevelopmental conditions, such as NGLY1 deficiency,[28] SYNGAP1-related intellectual disability,[34] and cerebral palsy.[35] These conditions, like Rett syndrome, are characterized by impairments in motor control, which can manifest in diminished movement fluidity and efficiency. The similarity of stride times, coupled with reductions in overall joint motion amplitude, may reflect compensatory mechanisms in motor control, where individuals trade off joint motion amplitude for maintenance of temporal gait consistency and postural control.

Phase portraits represent the control of an individual joint. The phase portraits shown in Figures 4 to 6 align with the reductions in range of motion and peak velocities presented in Tables 4 and 5. However, they further demonstrate that these reductions occur throughout the entire gait cycle. This is quantitatively confirmed by the significant decreases in phase portrait areas reported in Table 7. Although the overall shapes of the participants' phase portraits are comparable to those of the Control group, the magnitude differs. In the Rett syndrome participants, both the joint amplitude and velocity are decreased throughout the gait cycle, relative to the neurotypical individual.

Angle-angle diagrams represent the degree of coordination between joints. Similarly, the angle-angle diagrams displayed in Figures 7 to 9 highlight the overall reduction in lower limb movement observed in individuals with Rett syndrome, while also illustrating preserved joint coordination between Rett syndrome and age-matched Controls. The coordination between the hip and knee in Rett syndrome participants is largely comparable to that of the Control group, despite noticeable differences in traditional linear gait measures. Similar to previous reports of individuals with genetic developmental disorders,[28] the ankle joint displayed greater variability across participants and that was also true in the current data. This resulted in the knee-vs-ankle angle-angle diagrams being more dissimilar relative to the neurotypical participants than the hip-knee diagrams were. The variability of the ankle joint across the Rett syndrome participants may reflect individual compensatory adaptations, to maintain functional gait patterns. The similarity in the coordination pattern of the hip and knee, despite limited overall movement amplitude, indicates that knee control is relatively preserved. If the knee displayed a disordered movement pattern, then the hip-knee angle-angle diagram would no longer resemble that of the Controls' diagram. This indicates the disruption in knee-ankle coordination primarily stems from an impaired ability to control the distal ankle joint in a manner similar to the Controls. This finding is not surprising as toe

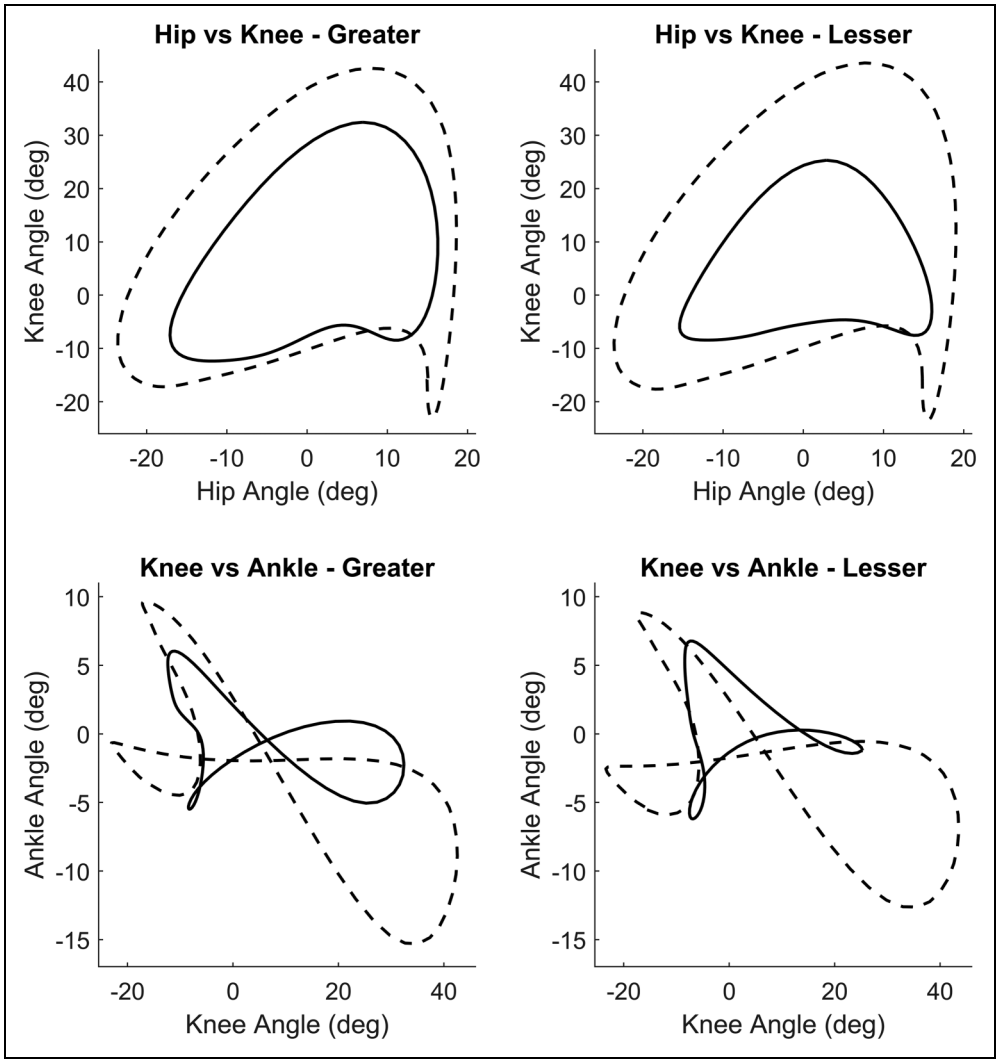

Figure 7. Rett vs Control angle-angle diagrams, 4-8 years old. Rett syndrome diagrams are shown in solid lines and Control diagrams are shown in dashed lines. The waveforms have been amplitude normalized to have a mean of zero, allowing for direct comparison of their relative shapes.

walking is often reported to be a gait feature of individuals with Rett syndrome.[6,15] The disruption in ankle control is consistent with a recent report of detailing gait features of individuals with NGLY1 Deficiency who also demonstrated similar difficulty at the ankle while maintaining hip and knee joint motion patterns similar to neurotypical individuals.[28]

The current study also identified the presence of asymmetries across multiple gait parameters in individuals with Rett syndrome. These asymmetries were evident in linear and nonlinear measures, indicating that individuals with Rett syndrome may not exhibit uniform motor control of both sides of the body. Asymmetry in gait has been previously reported in genetic developmental disorders like Rett syndrome[12] and SYNGAP1-Related Intellectual Disability.[34] In Rett syndrome, the observed asymmetries may reflect underlying disruptions in neural coordination. Although scoliosis could contribute to asymmetric movement patterns, participants with severe scoliosis did not exhibit asymmetries that were markedly greater than those of other participants. It has been reported that severe scoliosis is not associated with increased differences in gait parameters compared with mild scoliosis.[36] This suggests that the severity of scoliosis alone may not account for the observed asymmetries. Additionally, it is likely that individuals with relatively severe scoliosis have developed adapted kinematic behaviors that function to minimize their gait asymmetries. The presence of the observed gait asymmetries in Rett syndrome are not only characterized by reductions in overall movement amplitude and velocity but also by a lack of bilateral coordination. It has been reported that nearly 80% of individuals with Rett syndrome veer both while walking on the treadmill and overground.[15] Producing consistent joint motion patterns

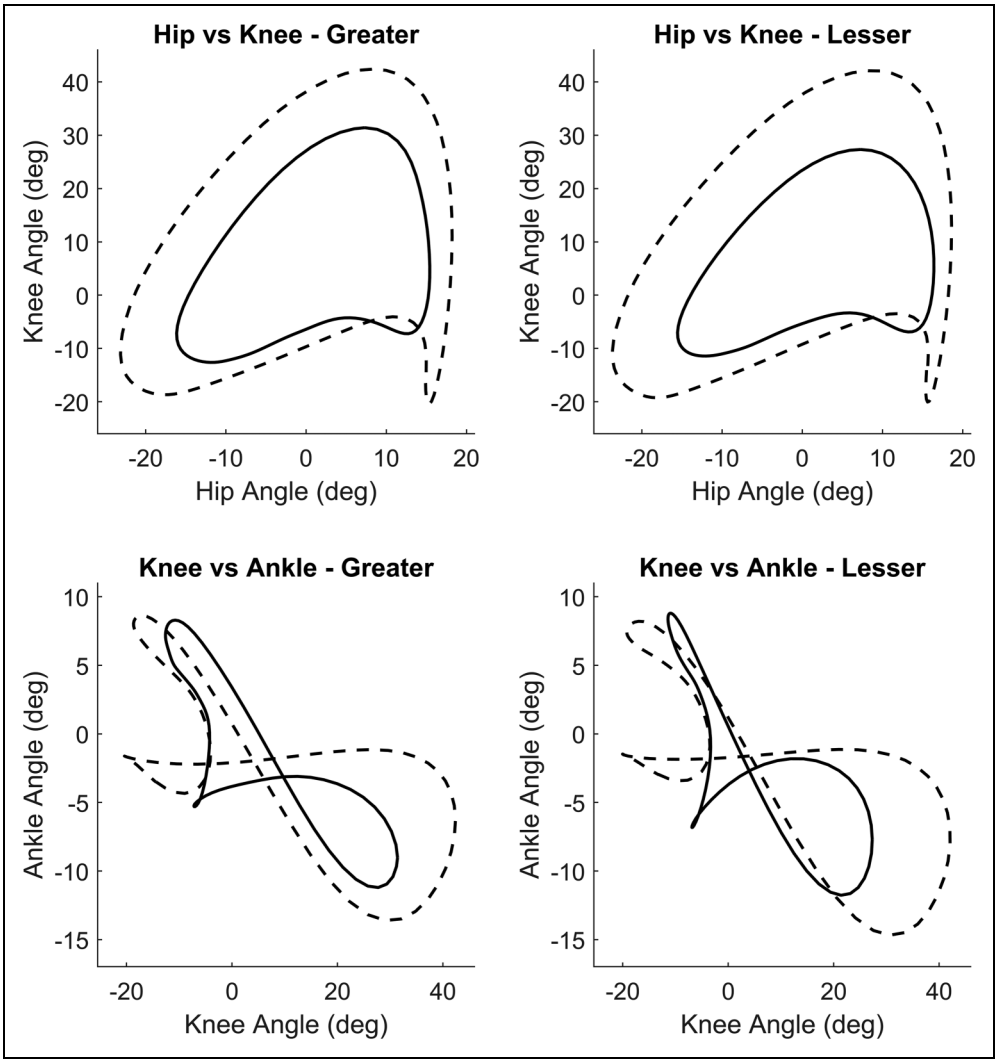

Figure 8. Rett vs Control angle-angle diagrams, 9-14 years old. Rett syndrome diagrams are shown in solid lines and Control diagrams are shown in dashed lines. The waveforms have been amplitude normalized to have a mean of zero, allowing for direct comparison of their relative shapes.

across both legs is essential to prevent veering and maintenance of straight-line gait. Moreover, the overall symmetry index provided additional information about the asymmetric behavior of the 2 limbs in the 9-14-year age group that was not evident in the more traditional measure of symmetry. Future work should explore the potential clinical implications of these asymmetries, as addressing them may be key to improving functional mobility and quality of life for individuals with Rett syndrome.

The only exception to the patterns observed in all metrics across joints and age groups was the ankle joint in the 9-14-year age group. Individuals with Rett syndrome in this age group showed ankle range of motion, ankle peak velocity, and ankle phase portrait areas similar to the age-matched Control group. This observed similarity in ankle movement between individuals with Rett syndrome aged 9-14 years and healthy individuals may reflect a unique developmental phase within the progression of Rett syndrome. This age range may correspond to a temporary period where gait may recover relative to the younger individuals with Rett syndrome before further deterioration in later adolescence and adulthood.[2,37] During this period, individuals with Rett syndrome might retain a level of motor control that allows for ankle movements more closely aligned with typical patterns. Additionally, the growth and muscular changes common in this age group could contribute to enhanced muscle tone, joint stability, and biomechanical efficiency, potentially facilitating greater ankle stability. This phenomenon may also be influenced by increased responsiveness to therapeutic interventions, which might be particularly effective at this stage because of higher motor adaptability. Furthermore, individuals with Rett syndrome in this age range may develop compensatory gait strategies that

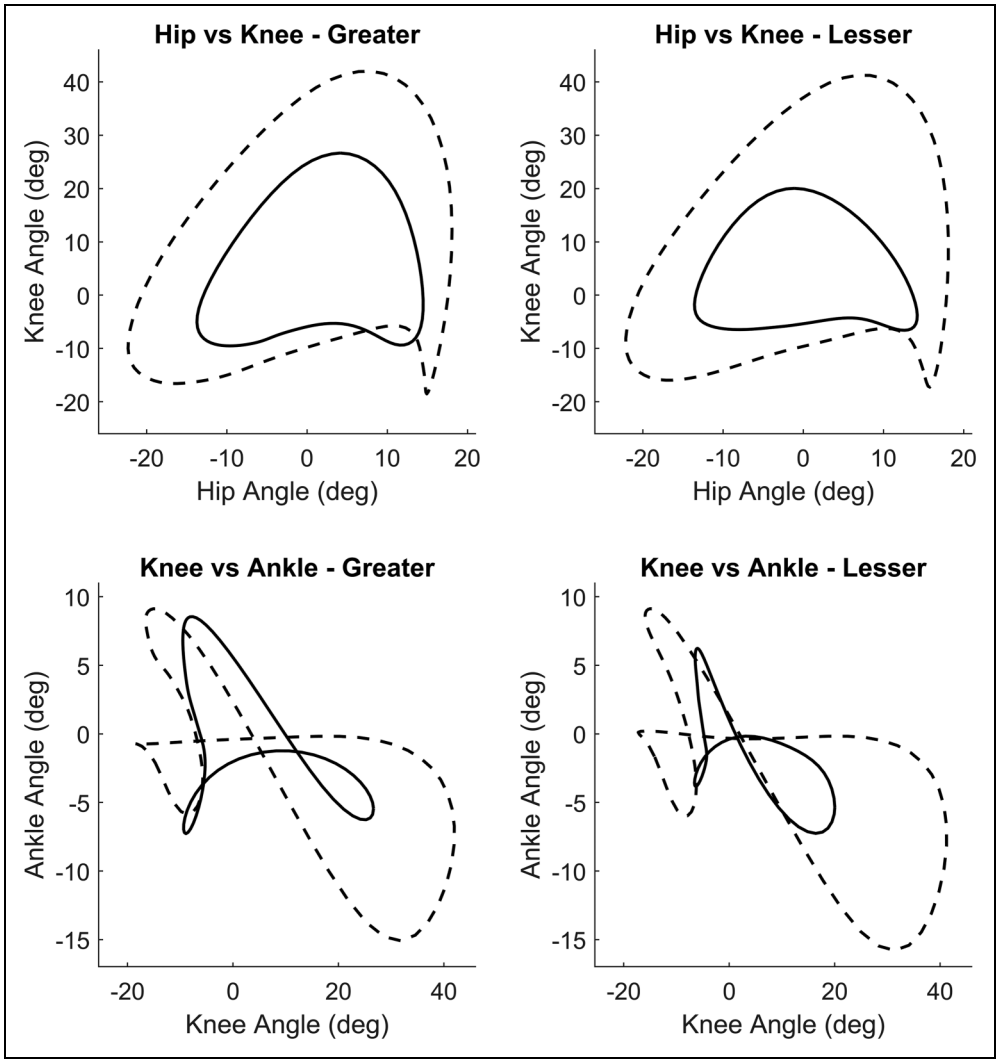

Figure 9. Rett vs Control angle-angle diagrams, ≥15 years old. Rett syndrome diagrams are shown in solid lines and Control diagrams are shown in dashed lines. The waveforms have been amplitude normalized to have a mean of zero, allowing for direct comparison of their relative shapes.

Table 8. Mean Angle-Angle Area by Age Group and Condition.

		Hip vs knee angle-angle area, degrees^2			Knee vs ankle angle-angle area, degrees^2		
Age group	Side	RTT, mean (SD)	Control, mean (SD)	Control, CI	RTT, mean (SD)	Control, mean (SD)	Control, CI
4-8 y	Greater	984.3 (167.4) *	1835.1 (278.1)	1642.4-2027.8	306.0 (120.5) *	484.0 (125.6)	397.0-571.0
	Lesser	731.9 (244.4) *	1748.3 (171.9)	1629.1-1867.4	180.7 (85.0) *	438.1 (89.9)	375.8-500.4
9-14 y	Greater	950.2 (260.3) *	1721.9 (321.9)	1464.4-1979.5	296.4 (178.9) *	498.3 (194.2)	342.8-653.7
	Lesser	830.9 (326.0) *	1681.8 (286.5)	1452.5-1911.1	258.3 (94.3) *	454.9 (125.3)	354.6-555.1
≥15 y	Greater	699.1 (237.5) *	1660.2 (195.3)	1524.9-1795.6	203.9 (76.8) *	524.8 (111.4)	447.6-602.1
	Lesser	493.0 (202.6) *	1548.6 (214.4)	1400.0-1697.2	129.4 (88.8) *	524.8 (135.2)	431.1-618.5
Age group		Hip vs knee angle-angle area Symmetry Index			Knee vs ankle angle-angle area Symmetry Index		
4-8 y		32.6 (20.2) *	7.9 (4.7)	4.7-11.2	52.7 (42.8) *	16.8 (11.2)	9.0-24.5
9-14 y		18.4 (17.0) *	4.6 (3.6)	1.7-7.5	21.8 (23.9) *	11.4 (12.4)	1.4-21.3
≥15 y		36.3 (34.7) *	9.5 (5.3)	5.8-13.1	52.6 (44.4) *	14.3 (8.9)	8.1-20.4

Abbreviation: CI, Confidence Interval; RTT, Rett syndrome.

help mitigate motor impairments, allowing for ankle movement patterns resembling those of typically developing individuals. In contrast, these similarities are less apparent in younger children, who may lack motor adaptability, and in older individuals, where progressive neuromuscular decline may overwhelm compensatory mechanisms.

The current findings must be interpreted considering certain limitations. Among these is the relatively small sample size within each age group, which constrained our ability to run more robust statistical analyses. Additionally, there was considerable intersubject variability between subjects within the Rett syndrome group. Although the data provided meaningful insights, both the small cohort and relatively high variability limit the generalizability of our findings. However, it should be kept in mind that individuals with Rett syndrome manifest a wide range of movement abnormalities, making it unrealistic to identify a 'stereotypical gait pattern' associated with Rett syndrome. Future studies with larger sample sizes will be essential to validate and extend these observations.

A manuscript assessing potential differences in kinematic features during gait of different age groups of individuals with Rett syndrome is in preparation. This will explore how motor impairments in Rett syndrome evolve over time and whether certain gait characteristics deteriorate or stabilize with age. Understanding these age-related changes will be critical in designing targeted interventions to support motor function across the lifespan of individuals with Rett syndrome.

Conclusions

This study provides a broad characterization of gait in individuals with Rett syndrome by using technology-based linear and nonlinear metrics and compares their gait characteristics with a control group of age-matched neurotypical individuals. Results revealed reduced joint range of motion in individuals with Rett syndrome, despite retaining waveform patterns similar to controls. Angle-angle diagrams and phase portraits indicated preserved coordination and motor control. However, the ankle demonstrated much greater variability in these measures. Asymmetries in gait parameters were identified, reflecting disruptions in bilateral motor coordination. The only exceptions to the differences between the Rett syndrome and Control individuals observed in all metrics across joints and age groups were the ankle joint metrics in the 9-14-year age group. Individuals with Rett syndrome in this age group showed ankle range of motion, peak velocities, and phase portrait areas similar to the age-matched Control group, possibly suggesting a unique developmental phase within the progression of Rett syndrome, where gait may recover relative to the younger individuals with Rett syndrome before further deterioration in later adolescence and adulthood. These findings enhance our understanding of gait in Rett syndrome and inform rehabilitation strategies by identifying motor deficits and their progression, supporting the development and evaluation of targeted interventions to improve mobility and quality of life in Rett syndrome.

Acknowledgements

We deeply appreciate the participants and their parents without whose efforts this work could not have been conducted. A special thanks to Alan El Hakam for his assistance during data collection.

ORCID iDs

Dacia Martinez Diaz https://orcid.org/0009-0003-2539-7585
Charles S. Layne https://orcid.org/0000-0001-6556-9896

Ethical Approval

Ethical approval for the study was obtained from the Institutional Review Boards of Baylor College of Medicine (Ethics Code: H-35835) and the University of Houston (ethics code: MODCR00000214) on June 19, 2017, and September 21, 2017, respectively.

Consent to Participate

Written informed consent for inclusion in this research was obtained from the parents of the participants.

Consent for Publication

Not applicable.

Author Contributions

DM and CSL were responsible for idea generation, data collection, data analysis, and manuscript development.
BS was responsible for idea generation; manuscript development; subject recruitment, including defining inclusion criteria; and funding acquisition.
BF collected and analyzed the data.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Funding for this research was provided by the Blue Bird Circle Rett Center, Houston, TX, and the International Rett Syndrome Foundation.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data Availability

The Rett syndrome data set generated and analyzed during the current study is available from the corresponding author on

reasonable request. The neurotypical Control data sets used in this study are openly available in the OSF.io repositories at http://doi.org/10.17605/OSF.IO/3XQEW and http://doi.org/10.17605/OSF.IO/T72CW.

Supplemental Material

Supplemental material is available upon request.

References

1. Petriti U, Dudman DC, Scosyrev E, Lopez-Leon S. Global prevalence of Rett syndrome: systematic review and meta-analysis. *Syst Rev*. 2023;12(1):5. doi:10.1186/s13643-023-02169-6
2. Neul NJL, Kaufmann WE, Glaze DG, et al. Rett syndrome: revised diagnostic criteria and nomenclature. *Ann Neurol*. 2010;68(6):944–950. doi:10.1002/ana.22124
3. Chapleau CA, Lane J, Pozzo-Miller L, Percy AK. Evaluation of current pharmacological treatment options in the management of Rett syndrome: from the present to future therapeutic alternatives. *Curr Clin Pharmacol*. 2013;8(4):358–369. doi:10.2174/15748847113086660069
4. Downs J, Leonard H, Jacoby P, Brisco L, Baikie G, Hill K. Rett syndrome: establishing a novel outcome measure for walking activity in an era of clinical trials for rare disorders. *Disabil Rehabi*. 2015;37(21):1992–1996. doi:10.3109/09638288.2014.993436
5. Pozzo-Miller L, Pati S, Percy AK. Rett syndrome: reaching for clinical trials. *Neurotherapeutics*. 2015;12(3):631–640. doi:10.1007/s13311-015-0353-y
6. Hanks SB. Motor disabilities in the Rett syndrome and physical therapy strategies. *Brain Dev*. 1990;12(1):157–161. doi:10.1016/s0387-7604(12)80201-4
7. Cass H, Reilly S, Owen L, et al. Findings from a multidisciplinary clinical case series of females with Rett syndrome. *Dev Med Child Neurol*. 2003;45(5):325-337. doi:10.1017/s0012162203000616
8. Downs JA, Bebbington A, Jacoby P, et al. Gross motor profile in Rett syndrome as determined by video analysis. *Neuropediatrics*. 2008;39(04):205–210. doi:10.1055/s-0028-1104575
9. Downs J, Stahlhut M, Wong K, et al. Validating the Rett Syndrome Gross Motor Scale. *PLoS One*. 2016;11(1):e0147555. doi:10.1371/journal.pone.0147555
10. Nomura Y, Segawa M. Characteristics of motor disturbances of the Rett syndrome. *Brain Dev*. 1990;12(1):27–30. doi:10.1016/s0387-7604(12)80170-7
11. Smeets EEJ, Pelc K, Dan B. Rett syndrome. *Mol Syndromol*. 2012;2(3-5):113–127. doi:10.1159/000337637
12. Layne CS, Young DR, Lee BC, Glaze DG, Schwabe A, Suter B. Kinematics associated with treadmill walking in Rett syndrome. *Disabil Rehabil*. 2021;43(11):1585–1593. doi:10.1080/09638288.2019.1674389
13. Temudo T, Ramos E, Dias K, et al. Movement disorders in Rett syndrome: an analysis of 60 patients with detected MECP2 mutation and correlation with mutation type. *Mov Disord*. 2008;23(10):1384–1390. doi:10.1002/mds.22115
14. Larsson G, Julu POO, Witt Engerström I, Sandlund M, Lindström B. Walking on treadmill with Rett syndrome—effects on the autonomic nervous system. *Res Dev Disabil*. 2018;83:99–107. doi:10.1016/j.ridd.2018.08.010
15. Young DR, Suter B, Levine JT, Glaze DG, Layne CS. Characteristic behaviors associated with gait of individuals with Rett syndrome. *Disabil Rehabil*. 2022;44(8):1508–1515. doi:10.1080/09638288.2020.1820084
16. Layne CS, Lee BC, Young DR, Glaze DG, Schwabe A, Suter B. Temporal gait measures associated with overground and treadmill walking in Rett syndrome. *J Child Neurol*. 2018. Published online January 1, 2018. doi:10.1177/0883073818780471
17. Lotan M, Gootman A. Regaining walking ability in individuals with Rett syndrome: a case study. *IJDHD*. 2012;11(2):163-169. doi:10.1515/ijdhd-2012-0020
18. Epstein A, Leonard H, Davis E, et al. Conceptualizing a quality of life framework for girls with Rett syndrome using qualitative methods. *Am J Med Genet A*. 2016;170(3):645–653. doi:10.1002/ajmg.a.37500
19. Palmieri M, Pozzer D, Landsberger N. Advanced genetic therapies for the treatment of Rett syndrome: state of the art and future perspectives. *Front Neurosci*. 2023;17:1172805. doi:10.3389/fnins.2023.1172805
20. Neul JL, Percy AK, Benke TA, et al. Trofinetide for the treatment of Rett syndrome: a randomized phase 3 study. *Nat Med*. 2023;29(6):1468–1475. doi:10.1038/s41591-023-02398-1
21. Goswami A. A new gait parameterization technique by means of cyclogram moments: application to human slope walking. *Gait Posture*. 1998;8(1):15–36. doi:10.1016/s0966-6362(98)00014-9
22. Di Giminiani R, Di Lorenzo D, La Greca S, et al. Angle-angle diagrams in the assessment of locomotion in persons with multiple sclerosis: a preliminary study. *Appl. Sci*. 2022;12(14):7223. doi:10.3390/app12147223
23. Hurmuzlu Y, Basdogan C, Carollo JJ. Presenting joint kinematics of human locomotion using phase plane portraits and Poincaré maps. *J Biomech*. 1994;27(12):1495–1499. doi:10.1016/0021-9290(94)90199-6
24. Neul NJL, Kaufmann WE, Glaze DG, et al. Rett syndrome: revised diagnostic criteria and nomenclature. *Ann Neurol*. 2010;68(6):944–950. doi:10.1002/ana.22124
25. Senden R, Marcellis R, Meijer K, et al. Dataset of 3D gait analysis in typically developing children walking at three different speeds on an instrumented treadmill in virtual reality. *Data Brief*. 2023;48:109142. doi:10.1016/j.dib.2023.109142
26. Senden R, Marcellis R, Willems P, Witlox M, Meijer K. Normative 3D gait data of healthy adults walking at three different speeds on an instrumented treadmill in virtual reality. *Data Brief*. 2024;53:110230. doi:10.1016/j.dib.2024.110230
27. Layne CS, Lee BC, Young D, Glaze DG, Suter B. Methodologies to objectively assess gait and postural control features in Rett syndrome: with a comment on specific challenges and how to address them. *RDODJ*. 2017;4(1):1–7.

28. Layne CS, Diaz DM, Malaya CA, et al. Using linear and non-linear techniques to characterize gait coordination patterns of two individuals with NGLY1 deficiency. *CRCM*. 2024;13(09):391–409. doi:10.4236/crcm.2024.139048.
29. Nigg S, Vienneau J, Maurer C, Nigg BM. Development of a symmetry index using discrete variables. *Gait Posture*. 2013;38(1):115–119. doi:10.1016/j.gaitpost.2012.10.024
30. Siebers HL, Alrawashdeh W, Betsch M, Migliorini F, Hildebrand F, Eschweiler J. Comparison of different symmetry indices for the quantification of dynamic joint angles. *BMC Sports Sci Med Rehabil*. 2021;13(1):130. doi:10.1186/s13102-021-00355-4
31. Colizzi M, Ciceri ML, Di Gennaro G, et al. Investigating gait, movement, and coordination in children with neurodevelopmental disorders: is there a role for motor abnormalities in atypical neurodevelopment? *Brain Sci*. 2020;10(9):601. doi:10.3390/brainsci10090601
32. O'Keefe JA, Robertson-Dick EE, Hall DA, Berry-Kravis E. Gait and functional mobility deficits in Fragile X-associated tremor/ataxia syndrome. *Cerebellum*. 2016;15(4):475–482. doi:10.1007/s12311-015-0714-4
33. Suzuki T, Ito Y, Ito T, et al. Pathological gait in Rett syndrome: quantitative evaluation using three-dimensional gait analysis. *Eur J Paediatr Neurol*. 2023;42:15–21. doi:10.1016/j.ejpn.2022.11.010
34. Layne CS, Malaya CA, Young DR, Suter B, Holder JL Jr. Comparison of treadmill gait between a pediatric-aged individual with SYNGAP1-related intellectual disability and a fraternal twin. *Front Hum Neurosci.* 2022;16:918918. doi:10.3389/fnhum.2022.918918
35. Johnson DC, Damiano DL, Abel MF. The evolution of gait in childhood and adolescent cerebral palsy. *J Pediatr Orthop*. 1997;17(3):392–396.
36. Mahaudens P, Banse X, Mousny M, Detrembleur C. Gait in adolescent idiopathic scoliosis: kinematics and electromyographic analysis. *Eur Spine J*. 2009;18:512–521. doi:10.1007/s00586-009-0899-7
37. Hagberg B. Clinical manifestations and stages of Rett syndrome. *Ment Retard Dev Disabil Res Rev*. 2002;8(2):61–65. doi:10.1002/mrdd.10020