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Lower-Limb Kinematic Coordination Strategies During Walking in Individuals with Rett Syndrome

Charles S. Layne[1,2], Dacia Martinez Diaz[1,2], Bernhard Suter[3,4]

[1]Department of Health and Human Performance, University of Houston, Houston, TX, USA.
clayne2@central.uh.edu
[2]Center for Neuromotor and Biomechanics Research, University of Houston, Houston, TX, USA.
dmart205@central.uh.edu
[3]Blue Bird Circle Rett Center, Texas Children's Hospital, Houston, TX, USA.
suter@bcm.edu
[4]Baylor College of Medicine, Houston, TX, USA.

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ABSTRACT

The kinematic gait patterns of individuals with Rett syndrome are often described as highly variable, yet the sources of this variability remain poorly understood. Traditional gait analyses typically summarize movement using discrete kinematic variables, which may obscure underlying patterns of coordination across the lower limbs. The purpose of this study was to apply principal component analysis to multi-joint lower-limb kinematics to identify underlying locomotor coordination strategies in individuals with Rett syndrome. Ten individuals with Rett syndrome walked on a treadmill while three-dimensional lower-limb joint kinematics were collected using a motion analysis system. After processing, the dataset consisted of 600 time-normalized strides (60 strides per participant). Principal component analysis was applied to the stride-by-feature matrix to identify coordinated patterns of joint motion across the lower limbs. Strides with similar principal component score profiles were grouped to define locomotor coordination strategies, and the biomechanical characteristics of each strategy were examined using waveform analysis. The analysis identified nine distinct coordination strategies across the 600 strides. Despite the presence of multiple strategies across the dataset, individual participants primarily relied on a single dominant strategy. Six participants produced the same strategy across all 60 of their analyzed strides, while the remaining participants also displayed strong dominance of one strategy. Further examination of joint excursion magnitude, peak-timing relationships, and inter-joint coordination patterns revealed that the nine strategies could be organized into three higher-level coordination families characterized by (1) constrained lower-limb excursion, (2) moderate excursion with altered timing relationships, and (3) plantarflexion-dominant propulsion patterns. These findings suggest that gait in Rett syndrome is produced through a limited set of biomechanical solutions rather than a single stereotypical gait pattern. Identifying these coordination strategies may provide a framework for understanding gait variability in Rett syndrome, guide individualized therapeutic interventions and potentially serve as a clinical biomarker for evaluating intervention effectiveness.

Introduction

Rett syndrome (RTT) is a rare neurodevelopmental disorder that predominantly affects females, with a prevalence of approximately 1 in 10,000 live female births worldwide. In roughly 95% of individuals with typical RTT, the condition is attributed to pathogenic variants in the methyl-CpG-binding protein 2 (MECP2) gene. Affected children initially demonstrate apparently typical development during the first 6–18 months of life, followed by a period of regression characterized by the loss of acquired motor, language, and social skills[1]. Clinically, RTT is associated with prominent impairments in fine and gross motor function, including stereotypical midline hand movements, hypertonia, apraxia, ataxia, disordered gait, and compromised postural control. Although a period of relative stabilization often follows regression, mobility frequently remains severely limited, with walking ability declining over time in many individuals. Previous investigation has found that approximately only half of those with RTT can walk[2] with 25% of ambulatory individuals requiring assistance[3]. Given the absence of curative treatment, there is a critical need for effective therapeutic interventions and the development of reproducible, quantitative clinical measures capable of sensitively detecting changes in motor function across research and clinical settings

Several investigations have characterized disordered gait observed in females with RTT, documenting a constellation of movement abnormalities that reflect impaired neuromotor control. Reported features include ataxic gait, toe walking, stiff-legged ambulation, freezing episodes, dysrhythmic stepping patterns, excessive lateral trunk motion, and the persistence of stereotypic hand wringing during walking[4,5]. Collectively, these behaviors suggest deficits in postural regulation, interlimb coordination, and motor planning.

Improving or maintaining the ability to ambulate is crucial for those with RTT. Impaired gait or complete loss of it is not merely a functional limitation; it is associated with secondary complications including limb contractures related to spasticity and immobility, muscle atrophy, scoliosis, and diminished overall physical and cardiorespiratory fitness. Physical activity engagement, including walking is central to physical health, wellbeing, and quality of life, including for those with RTT[6,7,8]. The recent approval of the first pharmacological treatment for Rett syndrome[9], along with ongoing gene-based therapy trials targeting functional improvement, underscores the urgent need for standardized, quantitative clinical outcome measures capable of reliable cross-site implementation. As therapeutic options expand, sensitive and reproducible metrics are essential to detect meaningful changes in gait performance. The development of technology-derived gait datasets in individuals with RTT represents a critical step toward establishing objective, quantitative biomarkers of the RTT motor phenotype[10]. Such information can also provide clinicians and therapists with robust tools to evaluate intervention efficacy across diverse research and clinical environments.

Recognizing the importance of standardizing measures, Downs and colleagues[11,12], advanced the field's understanding of functional motor capacity in RTT by implementing a surveillance video–based movement analysis protocol, allowing motor behaviors to be examined within naturalistic environmental contexts. Similarly, Young and colleagues[5] applied structured video analysis methodologies to further delineate walking-associated behaviors during both overground and treadmill ambulation, thereby providing complementary insights into gait performance across task demands.

To date there remains little research providing studies reporting quantitative results obtained with laboratory-based motion capture equipment. However, Layne and colleagues have authored several reports that provide temporal gait measures and joint kinematics obtained from individuals with RTT while walking both on a

treadmill, and in some instances, overground. These reports indicate that temporal measures such as stance, swing, and double support times differed between treadmill and overground walking and these values differed from aged-matched controls' data[13,14,15]. These authors also reported that lower limb joints angles and peak velocities increased with increasing treadmill speed, but their joint range of motions (ROM) were substantially less than that of neurotypical controls. A more recent report assessed potential kinematic differences between neurotypical aged-matched control and individuals with RTT during treadmill walking and found that lower limb joint ROMs and peak joints velocities were different across all age groups[14]. These linear measures were also consistent with the non-linear measures of angle-angle diagrams and joint phase portraits (i.e. joint angle verses its velocity through the gait cycle). These last two measures displayed considerable compression in the RTT data when compared to the control data, despite similar treadmill speeds. In the above studies, both mean symmetry of the two legs and variability measures far exceed those of neurotypical controls, regardless of the temporal or kinematic outcome variable being reported.[14]

The fact that variability measures were significantly elevated relative to neurotypical gait matches that readily apparent from visual inspection. Such variability may suggest that individuals with RTT are not producing a single stereotypical kinematic pattern but instead may rely on different underlying coordination strategies that vary across individuals. Indeed, visual inspection and structured observational video analyses indicate that stereotypical gait features are not consistently present across individuals with RTT[5]. This differs from 'Parkinsonian'[16,17], post-stroke[18,19], and cerebellar ataxia[20] gait, all of which display kinematic features unique to their underlying pathophysiology.

Historically the preponderance of gait kinematic reports has exclusively focused on sagittal plane motion, which is reasonable given that it is the primary plane of gait progression. Moreover, much of this work has primarily utilized linear measures such as individual joint range of motions, maximum and minimum joint values within a gait cycle, and joint velocity measures. However, gait is inherently multi-planar and requires coordinated motion across sagittal, frontal, and transverse planes[21].

In ambulatory neurological populations, atypical gait patterns frequently extend beyond isolated joint deviations and instead reflect altered inter-joint coordination. Analytical approaches that examine joints independently may therefore fail to capture the integrated structure of these abnormalities. Principal component analysis (PCA) has been widely applied in gait research to characterize coordinated kinematic patterns during walking by identifying dominant patterns of joint motion that occur consistently across joints and throughout the gait cycle. PCA-based approaches have been used to describe whole-body gait structure in neurotypical participants[22], as well as to identify altered coordination patterns in stroke [19,23], cerebral palsy[24,25], and Parkinson Disease[17]. Collectively, these studies demonstrate that multivariate decomposition techniques are well suited for isolating coordinated movement strategies that reflect underlying neuromotor constraints rather than independent joint-level abnormalities. Accordingly, we applied PCA to identify dominant coordination strategies while walking in ambulatory individuals with RTT. This enabled us to explore whether common coordination strategies are utilized across individuals RTT during walking. Conversely, if multiple coordination strategies are expressed across different RTT participants, this indicates that individualized interventions designed to modify specific features of joint motion should be considered by therapists and clinicians.

The purpose of this study was to apply principal component analysis to multi-joint lower-limb kinematics in individuals with RTT to identify underlying locomotor coordination strategies and

examine how these strategies are expressed across participants.

Methods

PARTICIPANTS

The participants were 10 females, all who had been diagnosed as have RTT using the criteria proposed Neul, et. al.[1] and expressing pathogenic variants in the MECP2 gene. All were patients at the Blue Bird Circle Rett Center at Texas Children's Hospital in Houston, TX. None were taking medications known to influence motor control and could walk independently without orthotics. Informed written consent was provided by the parents, and the study was approved by the Institutional Review Boards of Baylor College of Medicine (H-35835) and the University of Houston (MODCR00000214),

Study Protocol

DATA COLLECTION

The task involved the participants walking on a dual-belt motorized treadmill (Bertec®) with embedded force plates beneath each belt. Prior to data collection, reflective markers were placed bilaterally on anatomical landmarks including the anterior and posterior superior iliac spines, lateral thighs, lateral femoral condyles, lateral shanks, lateral malleoli, heels, and first metatarsophalangeal joints, enabling the capture of bilateral multiplanar hip, knee, and ankle kinematics. Participants were secured in an overhead safety harness that eliminated the risk of falls without providing postural support, thereby allowing unrestricted movement during walking.

During data collection, the participants walked at their comfortable speed. This speed was determined by initially setting the treadmill speed to 0.1 m/s and increased every 20 seconds by 0.1 m/s until the participants reached their maximum walking speed. This speed was identified when the participants began to express observable signs of discomfort such as hand and facial expressions or vocalizations, or their parents indicated the speed should be reduced. The treadmill speed was then decreased by 0.2 m/s and labeled as the participant's comfortable walking speed. The participants were provided with a brief rest, followed by data collection that involved up to three minutes of walking at the identified comfortable speed. Kinematic data were collected at 100 Hz using a 16-camera VICON® motion capture system and processed in Nexus software with the Plug-in Gait model to compute lower-limb joint angles.

DATA PROCESSING

All signal processing and analyses described in this section were conducted using custom MATLAB scripts. Three-dimensional bilateral hip, knee, and ankle joint angles were extracted and low-pass filtered using a second-order Butterworth filter with a 6 Hz cutoff frequency. Time series angle waveforms for each joint were partitioned into individual strides using peak knee flexion as the reference event. Right peak knee flexion was selected as a consistent kinematic feature that was used to segment each stride. This feature was used due to the occasional absence of heel strikes associated with toe walking observed during the walking period used to determine the comfortable walking speed[14,25,26]. In this investigation, gait was conceptualized as a bilateral coordination task; kinematics from both the right and left limbs were therefore segmented using the right peak knee flexion as a common stride reference. This contrasts with the more typical approach in which right and left stride kinematics are segmented independently using limb-specific gait events, most commonly heel strike of the respective limb.

Each participant walked between 70 and 110 strides, depending upon their comfortable speed. Each identified gait cycle was time-normalized to 100 samples to standardize stride duration across participants and enhance inter-subject comparability. To reduce inter-subject variability while preserving waveform shape characteristics, each individual waveform was mean centered by subtracting its average value from every sample

point. During data collection, some participants occasionally stumbled, briefly stepped off the treadmill belt, or completely stopped walking for a moment. As the purpose of this investigation was to use PCA to identify coordination strategies during gait, we considered such events as artifacts. Therefore, using every joint and dimension of each participant the time series waveforms were evaluated to identify outliers using a three standard deviation criterion. Outlier strides were subsequently removed from the data set of each participant, thereby providing a 'clean' data set free of outliers. To ensure that all participants contributed the same number of strides to the PCA analysis, a group data set composed of the first 60 strides of the clean data set for each participant was developed. A total of 600 strides were included in the PCA analysis (10 participants × 60 strides), with each stride consisting of three-dimensional bilateral hip, knee, and ankle joint angles. For each stride, the time-normalized joint angle waveforms were combined across all joints and planes for analysis[22,27]. To ensure that joints with larger ranges of motion did not disproportionately influence the analysis, all waveform samples were standardized using z-score normalization prior to principal component analysis.

PRINCIPAL COMPONENT ANALYSIS

To identify the dominant coordination structure, principal component analysis was applied to the stride-by-sample matrix, consistent with prior applications of PCA to multi-segment gait kinematics[17,27, 28]. In this framework, each principal component represents a coordinated strategy of movement variability across the lower limbs. The number of retained components was determined using the elbow method applied to the scree plot (a graph of the variance explained by each component), selecting the point beyond which additional components contributed minimal variance[29].

To facilitate biomechanical interpretation, joint contributions to each retained component were quantified by averaging the magnitude of loadings across time samples within the time-normalized gait cycle, and the most influential joints were identified. Each stride was then characterized by its principal component scores, reflecting how strongly it expressed each coordination pattern. Strides with similar score profiles were grouped together, and each resulting group was defined as a coordination strategy. Following identification of coordination strategies, the dataset was reorganized according to strategy assignment to enable subsequent waveform analysis. For each joint, descriptive statistics were computed across strides within each strategy, including the mean waveform and associated variability (standard deviation and 95% confidence intervals), providing standardized waveform summaries for each coordination strategy.

Strategy usage was quantified for each participant by tabulating the number and proportion of strides (out of 60 strides) classified into each strategy. Strategy frequencies were also aggregated across participants to characterize the overall distribution of coordination strategies.

Finally, strategy labels were derived from the collective biomechanical function of the five most strongly contributing joints and associated movement plane within each strategy. Joint contributions were interpreted in terms of movement amplitude (range of motion), timing of peak motion, and inter-joint coordination (coordinated timing and direction of motion across contributing joints). These features were used to determine whether each strategy was predominantly proximal or distal, organized along the sagittal chain, driven by rotational mechanics, or characterized by reduced excursion across contributing joints.

Results

Clustering of principal component scores identified nine lower-limb coordination strategies

across the 600 analyzed strides. Table 1 lists the participants, the nine identified coordination strategies, the total number of strides assigned to each strategy, and the percentage of the total strides represented by each strategy for each participant. Strategy usage was highly consistent within individuals. Six participants produced the same coordination strategy for all their 60 strides, while the remaining four participants still showed strong dominance of a single strategy (77–97% of strides). These results indicate that although multiple coordination strategies were identified across participants, individual participants primarily relied on a single dominant coordination strategy.

Importantly, clustering was performed using stride-level data, and the PCA algorithm was not informed which participant produced each stride. Despite this, strides were grouped primarily according to participant, indicating that participant-specific coordination patterns were sufficiently distinct to emerge naturally from the kinematic data.

Table 1: Strategies, strides, and the percentage of the total strides associated with a given strategy for each participant*.

Participant	Strategy	# Strides	%	Strategy	# Strides	%
1	8	60	100			
2	4	46	76.7	2	14	23.3
3	1	60	100			
4	2	60	100			
5	9	53	88.3	2	5	8.3
6	5	58	96.7	2	2	3.3
7	3	60	100			
8	7	60	100			
9	6	60	100			
10	1	56	93.3	4	4	6.7

*Participant 5 produced one stride classified as Strategy 1 and one stride classified as Strategy 7.

Table 2 displays each strategy, the number of strides that produced that strategy and the percentage of the total strides represented by each strategy, collapsed over participants. It can be observed that Strategy 1 was used for almost 20% of all strides which is almost double the other strategies, except for Strategy 2 (13.5%). Strategy 1 was used for 100% of the strides of Participant 3 and for 93% of the strides for Participant 10, which accounts for the relatively high percentage usage.

Table 2: Frequency and Percentage of Strides Producing Each Coordination Strategy

Strategies	Total Strides	Percentage
1	117	19.5
2	81	13.5
3	60	10
4	50	8.3
5	58	9.7
6	60	10
7	61	10.2
8	60	10
9	53	8.8
Total	600	100

Inspection of joint range-of-motion (ROM), peak-timing features, and inter-joint coordination relationships revealed that the nine identified strategies could be organized into three higher-level coordination families characterized by (1) constrained lower-limb excursion, (2) moderate excursion with altered timing relationships, and (3) high-excursion plantarflexion-dominant patterns. Figure 1 displays a representative strategy for each of the three families. These families were identified based on similarities in joint excursion magnitude, the timing of peak motion within the stride, and the relative contribution of proximal versus distal joints to the overall coordination pattern. The representative sagittal-plane joint waveforms were selected because they best illustrate the key biomechanical features that distinguish the coordination families.

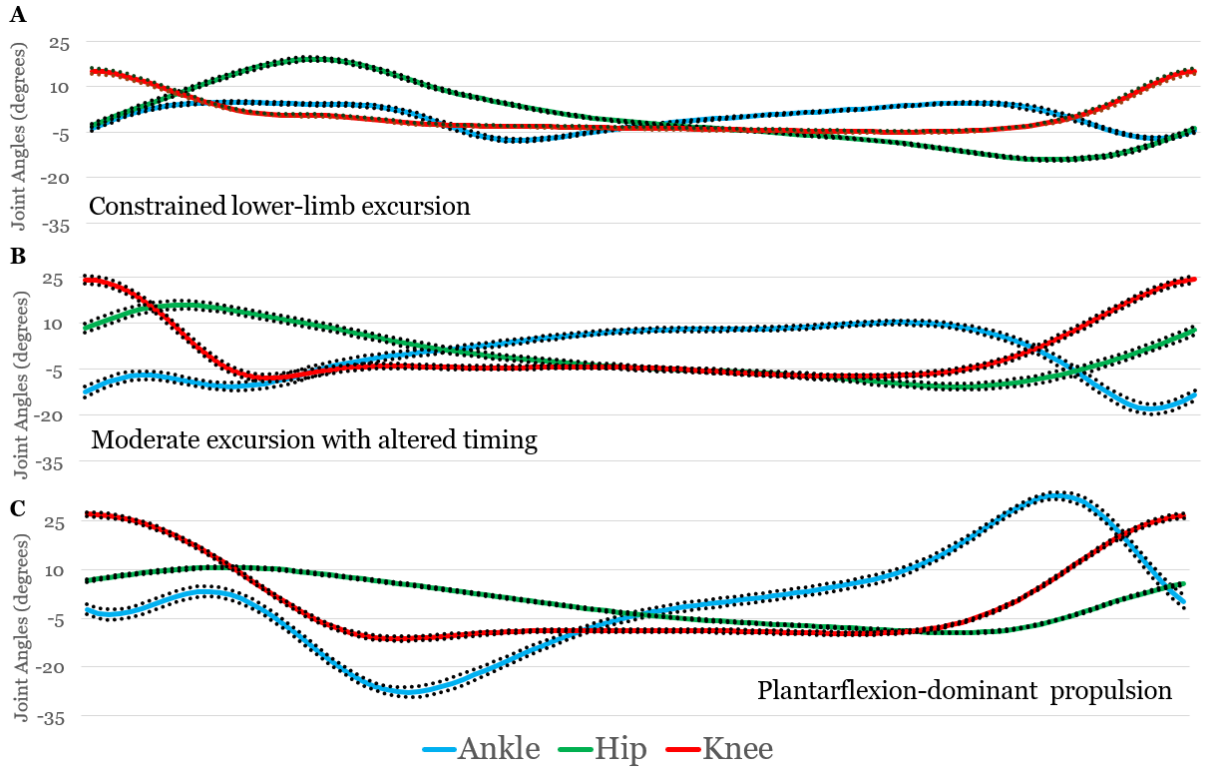

Figure 1. Representative right lower limb sagittal-plane joint waveforms illustrating the characteristic features of the three coordination families identified in the PCA analysis. Panel A shows a representative strategy from Family 1 (Strategy 2), Panel B shows a representative strategy from Family 2 (Strategy 3), and Panel C shows a representative strategy from Family 3 (Strategy 8). Mean joint waveforms are shown with shaded regions representing 95% confidence intervals computed across strides within each strategy.

Panel A shows a representative strategy from Family 1, characterized by relatively constrained sagittal-plane motion across the lower-limb joints, with modest hip and knee excursions and limited ankle plantarflexion during late stance. In contrast, Panel B displays a representative strategy from Family 2, in which lower-limb motion remains moderate but the hip, knee, and ankle waveforms show altered timing relationships across the stride compared with Family 1. Panel C illustrates a representative strategy from Family 3, which is distinguished by pronounced ankle plantarflexion during late stance, with substantially greater ankle excursion than observed in Families 1 or 2, indicating a locomotor pattern dominated by distal propulsion. Together, these waveforms illustrate the distinct joint behaviors that differentiate the coordination families and highlight the biomechanical patterns that define each family of coordination strategies.

Table 3 displays the dominant coordination strategy produced by each participant and the corresponding coordination family to which each strategy belongs.

Table 3. Dominant locomotor coordination strategy and corresponding coordination family for each participant*

Participant	Dominant Strategy	Secondary Strategy
Family 1		
3	1	
10	1	4
4	2	
2	4	2
8	7	
5	9	2
Family 2		
7	3	
9	6	
Family 3		
6	5	2
1	8	

*Participant 5 produced one stride classified as Strategy 1 and one stride classified as Strategy 7.

Consistent with the clustering results, most participants relied on a single dominant coordination strategy belonging to one of the three coordination families.

Discussion

The present study used principal component analysis (PCA) of lower-limb joint kinematic waveforms to identify coordination strategies while walking in individuals with RTT. Analyses of 600 strides obtained from 10 participants revealed nine distinct coordination strategies that could be further organized into three broader coordination families based on similarities in hip, knee, and ankle kinematic patterns. Although multiple coordination strategies were present across participants, most individuals expressed a single dominant strategy across the majority of their strides, indicating that gait in this sample of RTT participant was not characterized by highly variable stride-to-stride coordination patterns. Instead, individuals tended to rely on a consistent locomotor coordination strategy while walking. These findings suggest that the gait variability often reported in RTT may reflect differences in coordination patterns between individuals rather than instability within individuals. The variability in identified coordination strategies is therefore not unexpected given the broad spectrum of motor and clinical phenotypes observed in RTT[5,11,30,31]. Moreover, previous reports have shown that sisters with Rett syndrome, including monozygotic twins born to the same parents, can exhibit substantially different developmental trajectories and clinical phenotypes[32,33,34]. The variability in gait coordination strategies observed across individuals in this study is therefore consistent with the wide range of motor and clinical phenotypes reported throughout the RTT literature.

Further examination of the identified strategies revealed that they could be organized into three higher-level coordination families distinguished by differences in lower-limb excursion, timing relationships among joints, and the relative contribution of proximal versus distal joints to propulsion. These families represent distinct biomechanical solutions for producing forward progression during walking and illustrate how similar locomotor goals can be achieved through different patterns of joint coordination.

The correspondence between the identified coordination families and clearly recognizable joint kinematic patterns indicates that the PCA-based clustering approach captured meaningful locomotor behaviors rather than arbitrary statistical groupings. Together, these results demonstrate that data-driven analysis of multi-joint kinematics can reveal underlying coordination patterns that help explain how individuals with RTT organize lower-limb motion during walking.

Notably, the plantarflexion-dominant strategies identified in Family 3 were produced by participants who exhibited toe-walking behavior during treadmill locomotion. Because PCA was applied to stride-level kinematic data without participant identifiers, the clustering algorithm grouped these strides together solely based on their joint kinematic patterns. The resulting coordination family was characterized by

pronounced ankle plantarflexion during late stance, consistent with a locomotor pattern dominated by distal propulsion. This observation suggests that the distinctive biomechanics of toe walking were sufficiently pronounced to emerge naturally from the kinematic analysis.

A key contribution of this study is the use of PCA to characterize gait coordination patterns using full joint kinematic waveforms rather than discrete gait events or mean joint angles. Traditional gait analyses often rely on group-averaged waveforms or isolated kinematic variables, which can obscure important differences in inter-joint coordination. By evaluating the structure of the entire time-normalized waveform, PCA allows distinct coordination patterns to emerge from the data, revealing locomotor strategies that may be masked by conventional averaging approaches. As walking requires coordinated motion across multiple joints and planes, PCA provides a useful framework for identifying patterns of shared movement variability across the lower limbs. Using PCA, investigators have identified distinct kinematic coordination patterns in individuals post-stroke[19,20], those with knee osteoarthritis[28], and individuals with Parkinsonian gait[17].

Previous studies have reported considerable variability in gait kinematics across individuals with RTT, including altered joint excursions, reduced walking stability, and atypical coordination patterns[14,15,25]. The present findings suggest that locomotor behavior in individuals with RTT is organized around a limited set of coordination solutions that are expressed consistently within individuals but differ across participants. By applying PCA to multi-joint, three-dimensional, kinematic waveforms, the present study provides a framework for identifying underlying coordination patterns that may help explain the variability commonly observed in RTT gait. Together, these findings demonstrate that analysis of multi-joint kinematic waveforms can reveal the underlying coordination strategies used by individuals with RTT to organize lower-limb motion during walking.

Several limitations of the present study should be considered. First, although a large number of strides were analyzed, the number of participants was relatively small, reflecting the rarity of the clinical population. Second, the analysis focused on lower-limb joint kinematics during treadmill walking, which may not fully represent locomotor behavior during overground walking in natural environments. Third, the identification of coordination strategies using PCA is influenced by the biomechanical variables included in the analysis and the characteristics of those variables. While PCA is effective for identifying dominant patterns of movement variability, including different variables could potentially yield somewhat different strategy classifications. Fourth, treadmill walking has been shown to reduce kinematic variability relative to overground walking [35,36]. As a result, applying a similar analysis to kinematic data collected during overground walking may reveal additional coordination strategies both across and within individuals with RTT. Finally, because joint kinematic waveforms from neurotypical walkers were not included in the analysis, the present study cannot determine whether any of the nine identified strategies represent atypical gait patterns relative to typical locomotor coordination.

Future work involving larger cohorts and additional biomechanical variables may further clarify the range of coordination strategies used by individuals with RTT. In addition, future research should examine whether coordination strategies identified through PCA remain stable over time, change with development, or respond to therapeutic intervention. Longitudinal investigations may help determine whether individuals transition between strategies as motor function evolves. Furthermore, applying similar analytical approaches to other neurological populations may provide insight into how different disorders influence locomotor coordination and whether common strategy patterns emerge across clinical conditions. Ultimately, identifying stable

coordination strategies may help guide the development of individualized therapeutic interventions tailored to an individual's locomotor patterns and may serve as clinical biomarkers for evaluating treatment efficacy.

Conclusions

The identification of subject-specific coordination strategies has potential implications for therapeutic interventions aimed at improving locomotor function in individuals with RTT. Traditional rehabilitation approaches often target generalized gait impairments across patients; however, the present findings suggest that individuals may rely on distinct coordination solutions to walk. Identifying a patient's dominant coordination strategy could therefore provide a basis for developing more personalized interventions that target specific joint coordination patterns. This approach may allow clinicians to tailor therapeutic strategies to the individual locomotor organization of each patient rather than assuming a uniform gait pattern across the population.

Conflicts of Interest Statement

The authors have no conflicts of interest to declare

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